WATCHMAN Left Atrial Appendage Closure (LAAC) Technology

FDA Review of P130013

Rachel Neubrander, PhD
Division of Cardiovascular Devices
Office of Device Evaluation
Food and Drug Administration

October 8, 2014

FDA Review Team Members

- Rachel Neubrander, PhD
- Andrew Farb, MD
- Manuela Buzoianu, PhD
- George Aggrey, MD, MPH

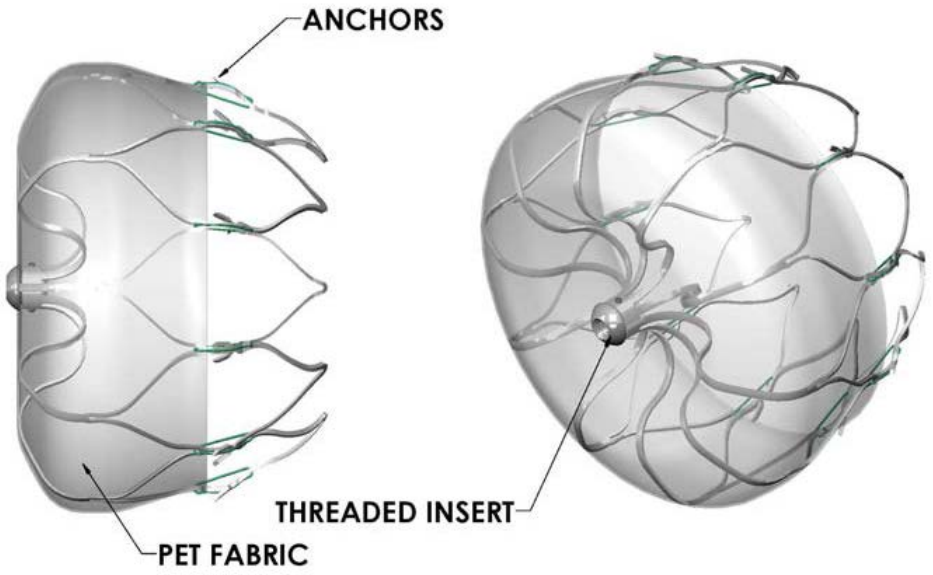
FDA Presentations

- Introduction and Regulatory History – Dr. Rachel Neubrander
- Clinical Presentation – Dr. Andrew Farb
- Statistical Presentation – Dr. Manuela Buzoianu
- Summary – Dr. Rachel Neubrander

Device Description

WATCHMAN LAAC Technology includes:

- WATCHMAN Implant (shown right, 5 sizes available)
- Delivery System (12 Fr)
- Access System (14 Fr)



Non-clinical testing is complete.

Proposed Indications for Use

Indications for Use:

The WATCHMAN LAAC Device is indicated to prevent thromboembolism from the left atrial appendage. The device may be considered for patients with non-valvular atrial fibrillation who, based on CHADS2 or CHA2DS2-VASc scores, would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism."

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Regulatory History

- PROTECT AF pivotal study approved in December 2005: randomized controlled trial to test non-inferiority of WATCHMAN device + short-term warfarin vs. chronic warfarin.
- PROTECT AF Continued Access registry (CAP) approved in 2008
- Original pre-market approval application (PMA) submitted in 2008

Regulatory History

- Circulatory System Devices Panel Meeting held April 23, 2009
- FDA raised the following concerns:
  - Confounding effects of concomitant antithrombotic use and subjects not receiving assigned treatment
  - Acute safety events: pericardial effusion, air embolism
- Panel voted 7 to 5 in favor of “Approvable With Conditions”
  - Concerns about lack of long-term data and discussion regarding safety

Regulatory History

- Not Approvable (NOAP) letter dated March 10, 2010.
- FDA and sponsor designed new study: PREVAIL
  - Approved in 2010.
  - Goal of both building on existing data and addressing limitations of PROTECT AF.
- Additional follow-up data from PROTECT AF and CAP not sufficient alone for approval, but still important.

Regulatory History

- Limitations of PROTECT AF addressed in PREVAIL included:
  - Included low risk patients
  - Potential confounding effect of concomitant clopidogrel use
  - Warfarin compliance and monitoring
- December 2013 panel
  - PREVAIL January 2013 dataset (11.8 ± 5.8 months mean follow-up)
  - Long-term PROTECT AF and CAP follow-up

Regulatory History

- Failed to meet the non-inferiority endpoint compared to warfarin for the composite of all stroke, systemic embolism, and CV or unexplained death (PREVAIL 1st primary endpoint)
  - The event rates for all of the individual components of the first primary endpoint (ischemic stroke, hemorrhagic stroke, systemic embolism, and CV/unexplained death) favored the Control group (PREVAIL-only subjects)

Regulatory History

- Met the non-inferiority endpoint compared to warfarin for ischemic stroke and systemic embolism events occurring after 7 days post-randomization (PREVAIL 2nd primary endpoint)
- Met the implant procedure-associated major event rate performance goal endpoint (PREVAIL 3rd primary endpoint)
- In PREVAIL, WATCHMAN device implantation was not associated with a signal of reduced overall bleeding events

Regulatory History

- New operators were able to successfully and safely implant the device at rates at least comparable to experienced operators
- PREVAIL showed that device implantation could be reasonably safe with an acceptable operator learning curve

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Panel voted 13 to 1 in favor of safety, effectiveness, and favorable benefit-risk profile

Why are we here?

- In response to an FDA request, the sponsor provided new follow-up data on PREVAIL patients beginning in February 2014 that showed new ischemic strokes in the WATCHMAN group
  - June 2014 database lock demonstrated an imbalance in ischemic stroke rate between the WATCHMAN and control groups (13:1 events), raising concern regarding device effectiveness

Why are we here?

Does the totality of the data change the previous conclusion of a favorable benefit-risk profile for the WATCHMAN device?

FDA Presentations

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- Clinical Presentation – Dr. Andrew Farb
- Statistical Presentation – Dr. Manuela Buzoianu
- Summary – Dr. Rachel Neubrander

FDA Clinical Review

Andrew Farb, M.D.
Division of Cardiovascular Devices
Center for Devices and Radiological Health

Outline

- The PREVAIL trial
  - Designed to address the limitations of PROTECT AF
  - 1st and 2nd primary endpoint results (Jan 2013 dataset)
- PREVAIL (only) trial update (June 2014 dataset)
  - New events
  - Impact on 1st and 2nd primary endpoint results
- Considering the WATCHMAN device within a benefit-risk framework
- Indications for Use statement
- Concluding remarks

Definition of Data Presentation Terms

- **PREVAIL Only** analyses are based on data limited to new subjects enrolled in the PREVAIL trial

- **PREVAIL or PREVAIL Bayesian** analyses are based on data that includes new subjects enrolled in the PREVAIL trial **plus** PROTECT trial data, down-weighted 50%

The PREVAIL Trial

The PREVAIL Trial

Designed to Address the Limitations of PROTECT AF Trial

- Enroll higher risk subjects by limiting inclusion to subjects with $CHADS_2$ ≥2 or $CHADS_2$ =1 with additional stroke risk factors (equivalent to CHA_2DS_2-VASc)
- Exclude subjects indicated for chronic clopidogrel therapy to reduce confounding
- Provide enhanced monitoring of warfarin use to increase compliance and INR control
- Reduce NI margin from 2.0 to 1.75 for the first primary endpoint

The PREVAIL Trial

Designed to Address the Limitations of PROTECT AF Trial

- Added a second primary endpoint to address LAA occlusion proof of concept
- Added a third primary endpoint to address WATCHMAN device implantation safety concerns
- Required participation of new operators and new clinical sites to address WATCHMAN device implantation learning curve

Leveraging PROTECT AF Safety and Effectiveness Data

- FDA recognized that, despite limitations, there was value in the PROTECT AF data
- FDA and the Sponsor developed a Bayesian study design for PREVAIL in which a portion of the PROTECT AF data would be used as an informative prior.
  - FDA and the Sponsor agreed that the prior PROTECT data from PREVAIL-eligible PROTECT subjects would be discounted 50% in the analysis of the first and second primary endpoints in PREVAIL.

PREVAIL Trial

- Objective: To demonstrate the safety and effectiveness of the WATCHMAN device for the prevention of ischemic stroke and systemic thromboembolism in subjects with non-valvular atrial fibrillation who are eligible for warfarin therapy
- Control: Warfarin
- Design: Randomized 2:1 – WATCHMAN:Control
- Statistical analysis of first and second primary endpoints to include prior data from PROTECT AF down-weighted 50%

Treatment Strategy – WATCHMAN Group

- WATCHMAN device was implanted into the LAA via atrial transseptal access.
- Post-implant, subjects treated with adjusted dose warfarin plus 81 mg aspirin.
- At 45 days (or 6 months) post-implant, if TEE showed LAA occlusion, warfarin therapy could be discontinued.
- Subjects who discontinued warfarin at day 45 were treated with 325 mg aspirin plus 75 mg clopidogrel through 6 months.
  - Clopidogrel was to be stopped at 6 months post-device implantation
  - 325 mg aspirin was to be continued indefinitely (destination therapy)

Treatment Strategy – Warfarin Group

- Either initiation or continuation of warfarin therapy for the duration of the trial
- Target INR of 2.0-3.0

PREVAIL Trial
Addressing the Limitations of PROTECT AF

WATCHMAN Group Subjects

- Lower rate of subjects who did not receive the device
  - 3.6% in PREVAIL vs. 11.9% in PROTECT
- Higher rate of warfarin discontinuation in PREVAIL at 45 days (92% vs. 87%) and 6 months (98% vs. 92%)
- Lower rate of long-term warfarin resumption
  - 4.8% in PREVAIL vs. 7.1% in PROTECT

Control Group Subjects

- High rate (≈83%) of documented compliance with monthly INR monitoring in PREVAIL
- No subjects who never started anticoagulation in PREVAIL vs. 3 subjects in PROTECT

PREVAIL Trial

Addressing the Limitations of PROTECT AF

Higher risk subjects enrolled

PROTECT AF	WATCHMAN	Control
$CHADS_2$ Score	2.2 ± 1.2	2.3 ± 1.2
CHA_2DS_2 VASc Score	3.2 ± 1.4	3.5 ± 1.5

PREVAIL Only	WATCHMAN	Control
$CHADS_2$ Score	2.6 ± 1.0	2.6 ± 1.0
CHA_2DS_2 VASc Score	4.0 ± 1.1	4.1 ± 1.2

PREVAIL Only Events

Jan 2013 Dataset, Dec 2013 Panel

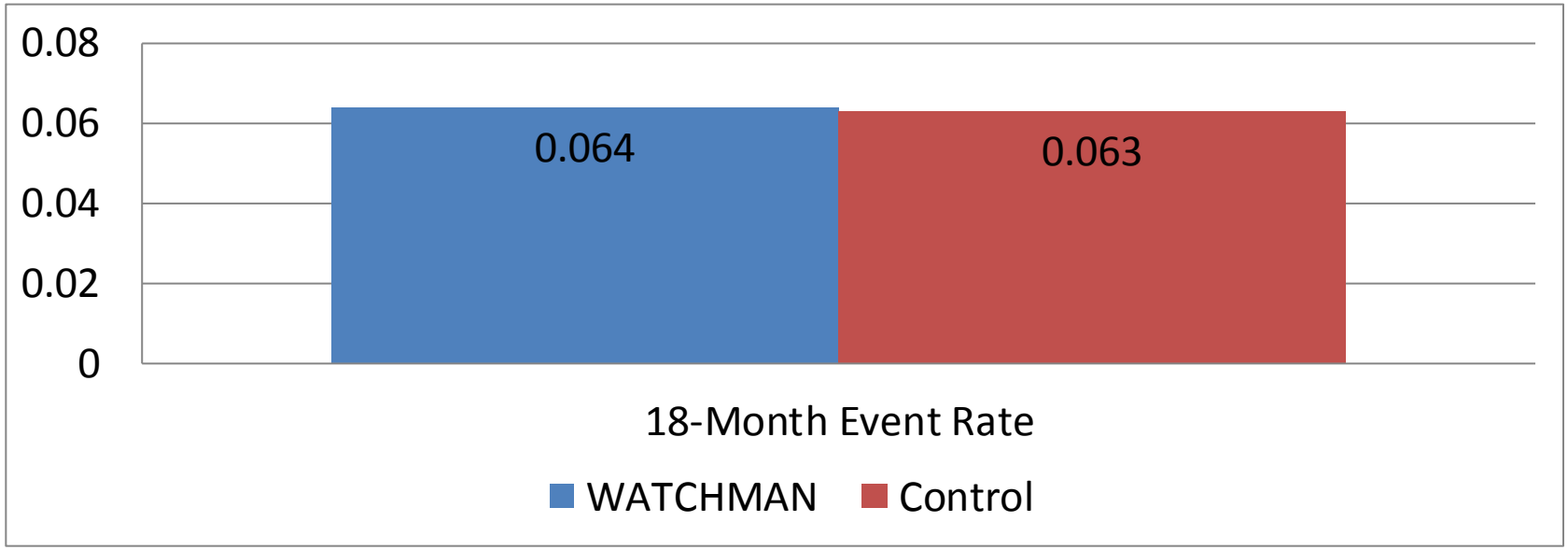
Events	WATCHMAN (n=269)			Control (n=138)		
	N Events	Rate Per 100 pt-yrs	Rate Per Patient	N Events	Rate Per 100 pt-yrs	Rate Per Patient
Stroke – Ischemic	5	1.94	1.9	1	0.71	0.7
Stroke - Hemorrhagic	1	0.39	0.4	0	0.00	0.00
Systemic Embolism	1	0.39	0.4	0	0.00	0.00
CV or Unexplained Death	7	2.70	2.6	3	2.13	2.2

2:1 Randomization – WATCHMAN:Control

Jan 2013 Dataset, Dec 2013 Panel

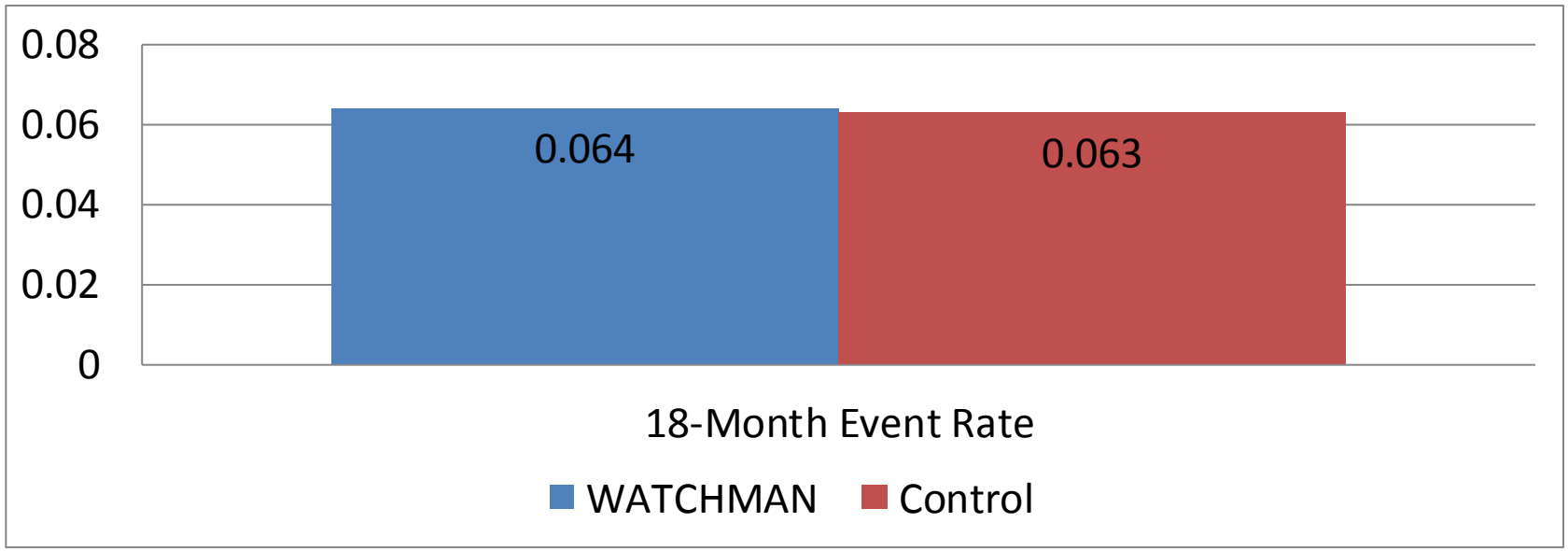
First Primary Endpoint:

All stroke, systemic embolism, or CV/Unexplained death

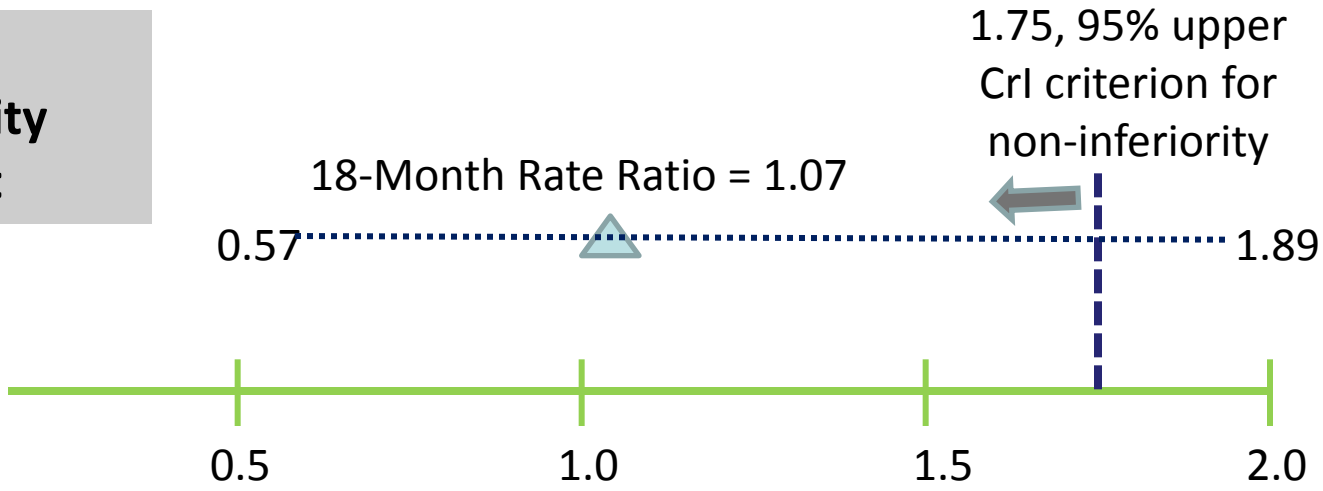


Bayesian Analysis 18 Month Rate

Jan 2013 Dataset, Dec 2013 Panel



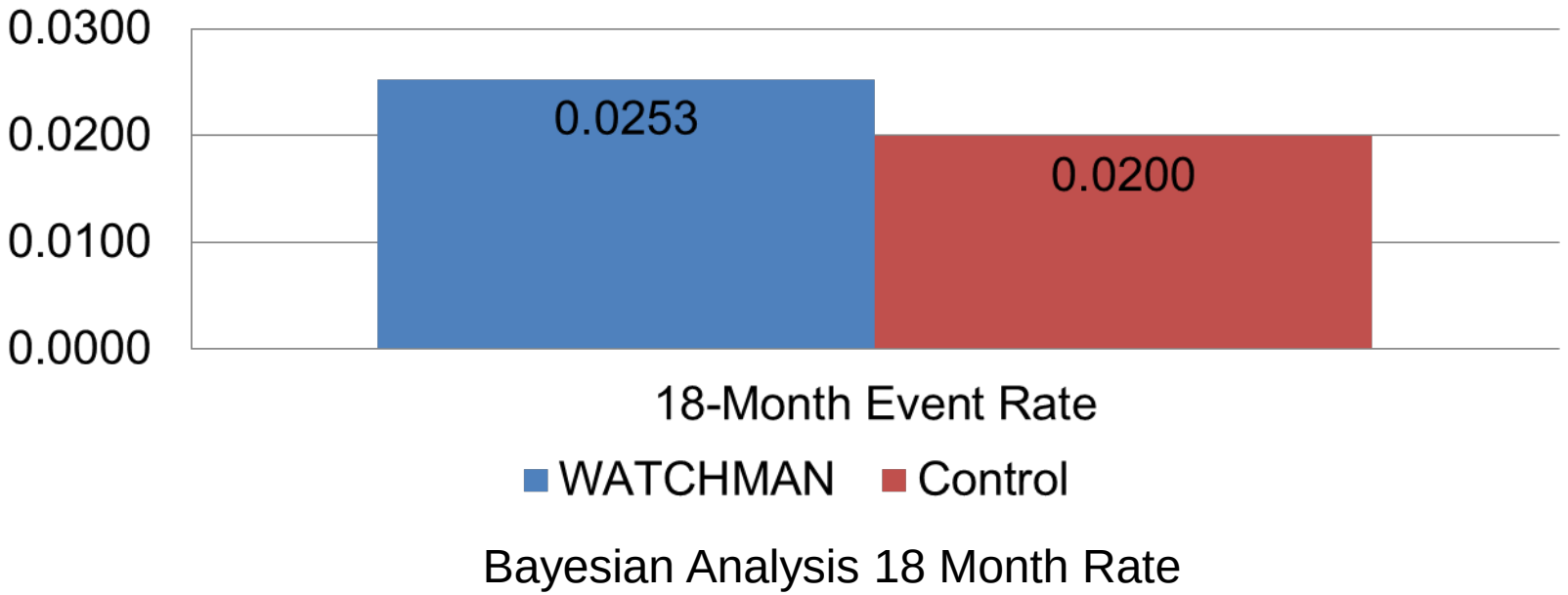
Non-inferiority not met



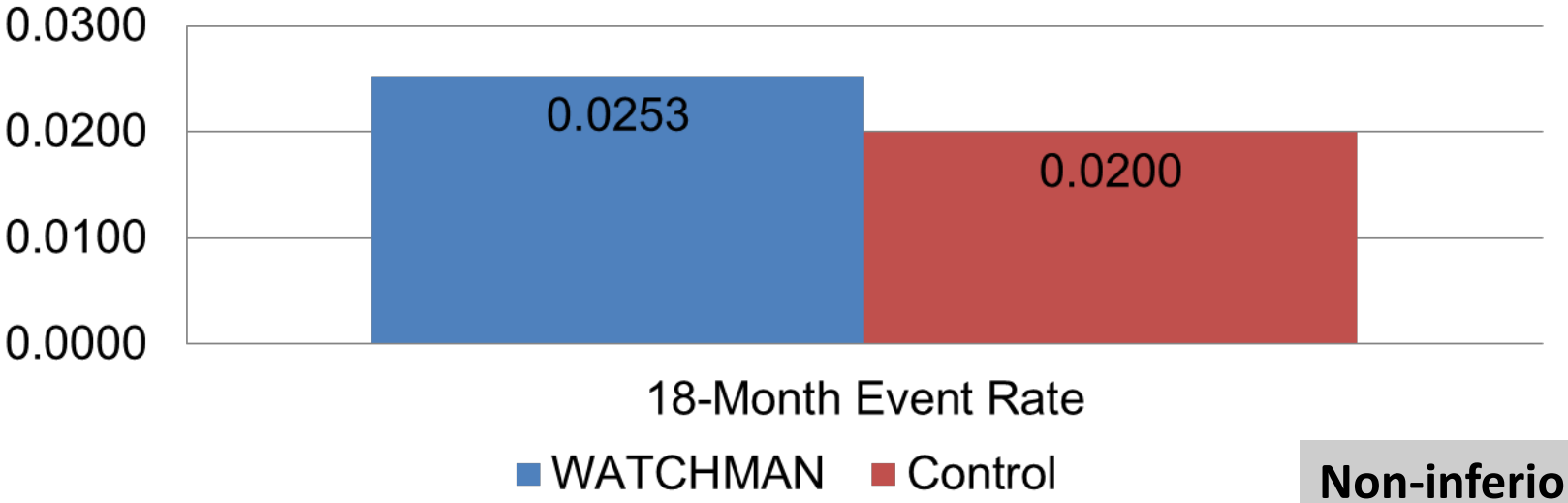
Jan 2013 Dataset, Dec 2013 Panel

Second Primary Endpoint:

Ischemic stroke or systemic embolism after the first 7 days post-randomization

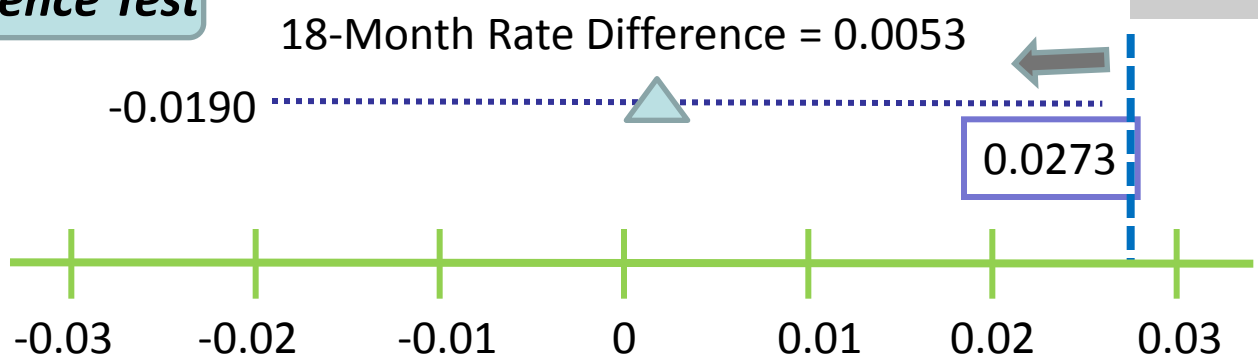


Jan 2013 Dataset, Dec 2013 Panel



Rate Difference Test

Non-inferiority met



January 2013 Dataset

- The ischemic stroke rate numerically favored the Control group in the PREVAIL Only dataset (consistent with PROTECT AF)
- Bayesian analysis of PREVAIL
  - Non-inferiority for the first primary endpoint not met
  - Non-inferiority for the second primary endpoint met for risk difference

January 2013 Dataset Caveats

- PREVAIL Only subjects
  - Mean duration of follow-up from the time of randomization was only 11.8 ± 5.8 months
  - Only 28% of subjects had reached or passed the 18-month follow-up window

Additional PREVAIL Only Events
Between January 2013 Dataset Lock and June 2014 Dataset Lock

Watchman Group

- **8 new ischemic strokes**
- 1 new hemorrhagic stroke
- 1 new cardiovascular or unexplained deaths

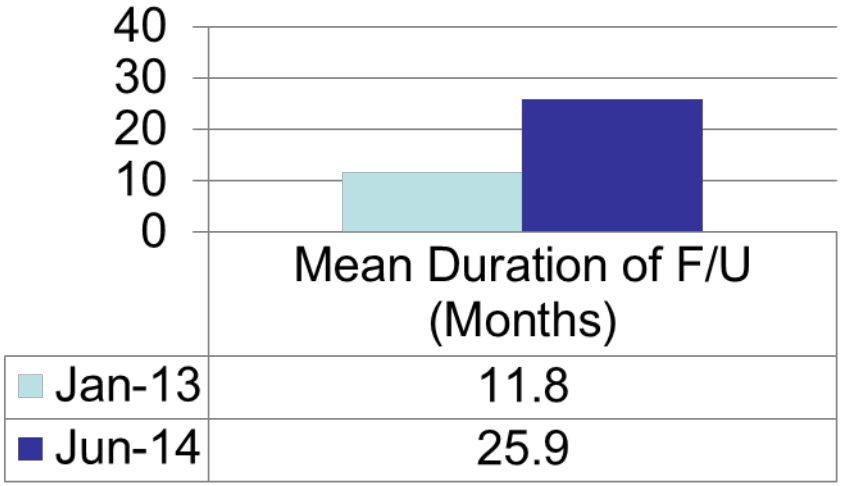
Control Group

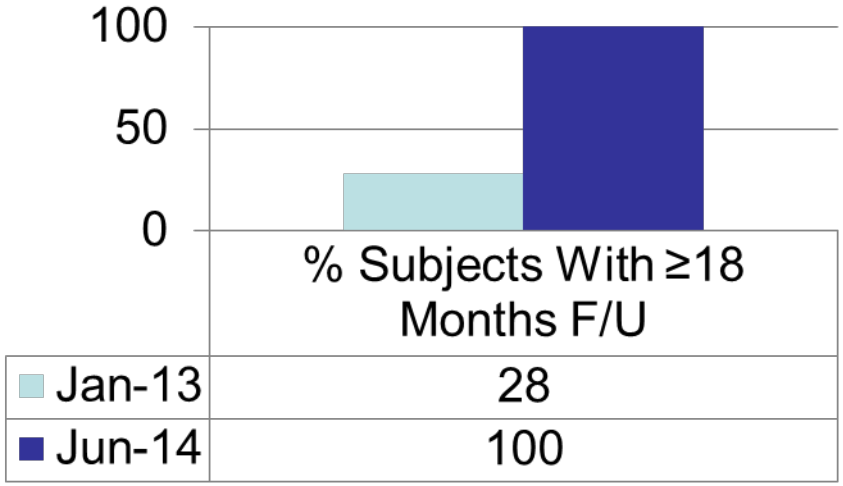
- 0 new ischemic strokes
- 2 new hemorrhagic strokes
- 3 new cardiovascular or unexplained deaths

2:1 Randomization WATCHMAN:Control

PREVAIL Only

From January 2013 to June 2014





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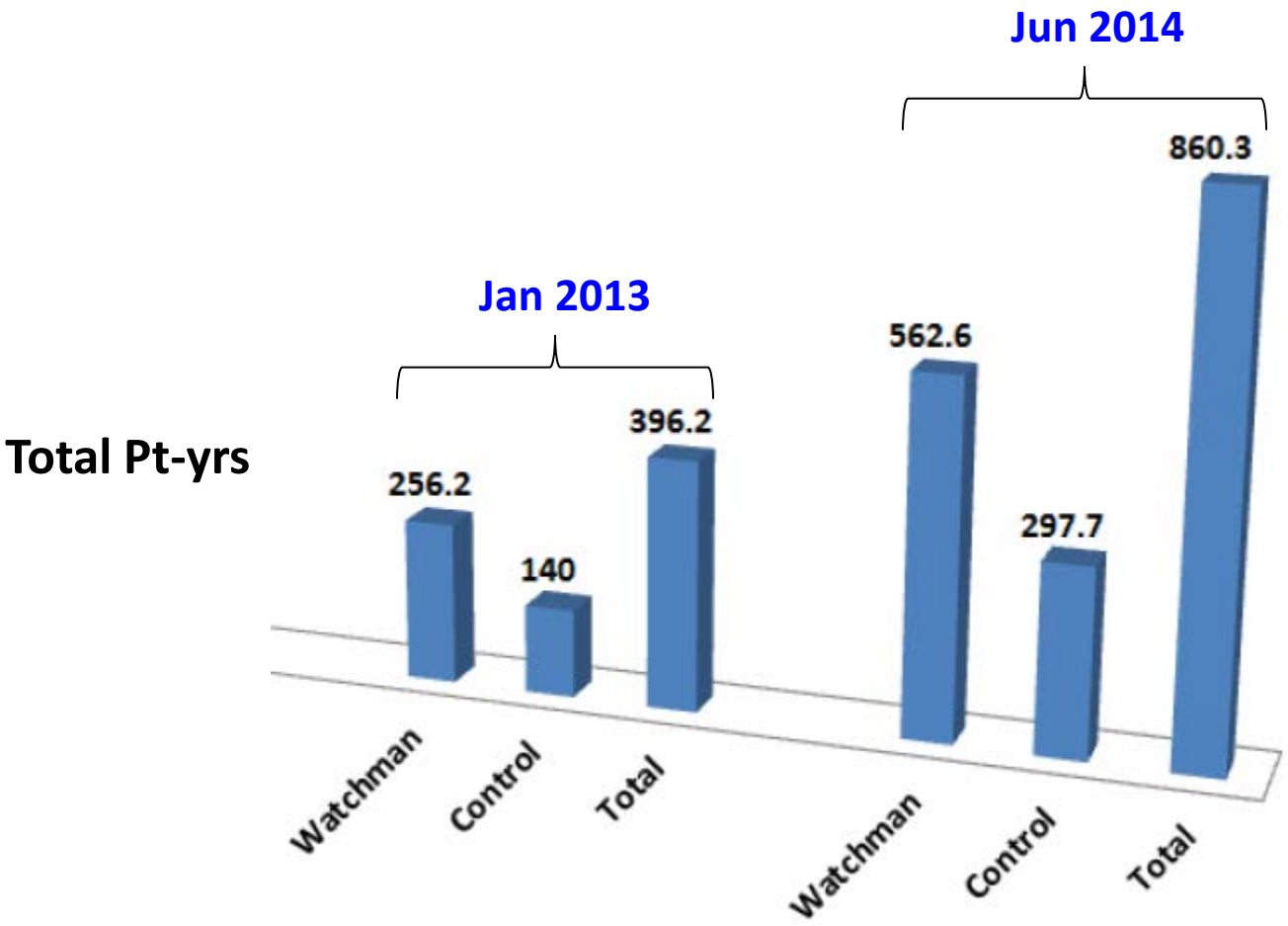

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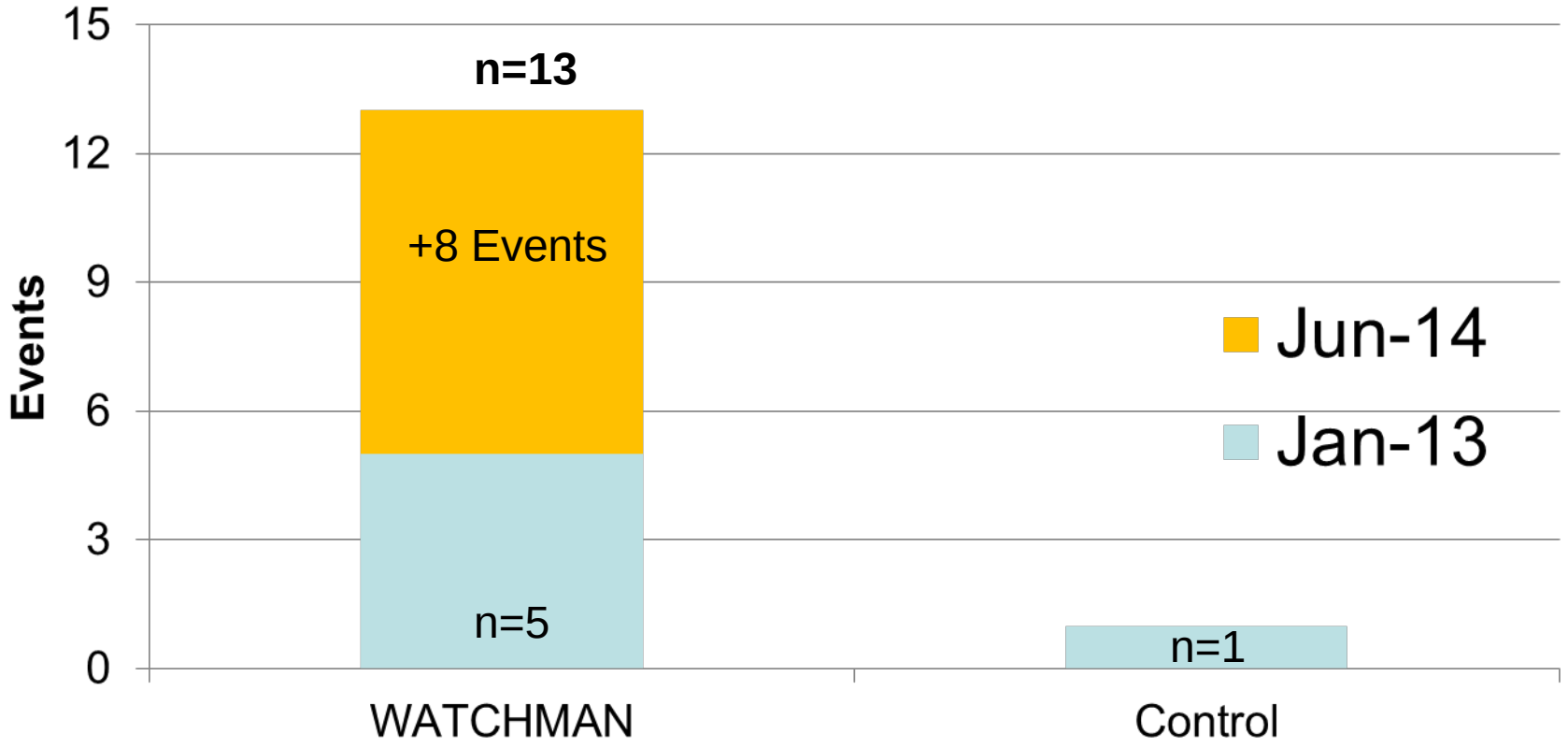
Ischemic Stroke Events



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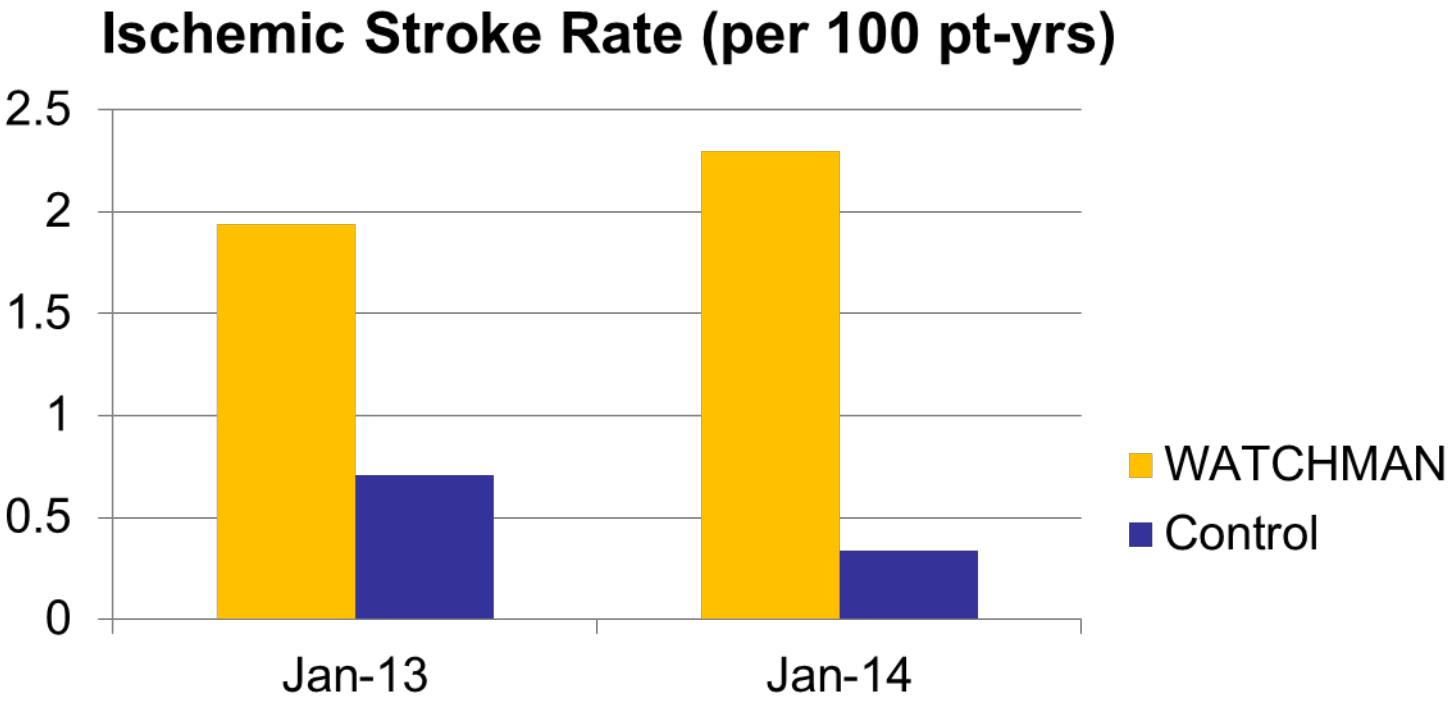

	Jan-13	Jun-14
WATCHMAN	1.94	2.3
Control	0.71	0.34

Impact of New Events on the Bayesian Analysis of PREVAIL's First and Second Primary Endpoints

PREVAIL First Primary Endpoint

All Stroke, Systemic Embolism, or CV/Unexplained Death

18 month rate Bayesian analysis

	18 Month Rate				Rate Ratio NI Criteria 95% CrI <1.75
Dataset	**Watchman**	**Control**	**Rate Ratio**	**95% CrI**	**NI Criteria Met?**
Jan 2013	0.064	0.063	1.07	0.57-1.89	No

CrI = Credible interval, NI = Non-inferiority

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Jun 2014	0.065	0.057	1.21		

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PREVAIL Second Primary Endpoint

Ischemic Stroke or Systemic Embolism
Occurring After the First 7 Days Post-Randomization

18 month rate Bayesian analysis: Rate difference

	18 Month Rate				Rate Difference NI Criteria 95% CrI <0.0275
Dataset	**Watchman**	**Control**	**Rate Difference**	**95% CrI**	**NI Criteria Met?**
Jan 2013	0.0253	0.0200	0.0053	-0.0190-0.0273	Yes

CrI = Credible interval, NI = Non-inferiority

PREVAIL Second Primary Endpoint

Ischemic Stroke or Systemic Embolism
Excluding the First 7 Days Post-Randomization

18 month rate Bayesian analysis: Rate difference

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Updated PREVAIL First and Second Primary Endpoint Results

- The WATCHMAN device did not meet non-inferiority vs. warfarin for:
  - All stroke, systemic embolism, or CV/unexplained death
  - Ischemic stroke or systemic embolism excluding the first 7 days post-randomization

Benefit-Risk Considerations

Framing Benefit - Risk

- Is implantation of the WATCHMAN device associated with an acceptable rate of procedure-related complications?
- Does the WATCHMAN device provide adequate protection from ischemic stroke or systemic embolism in at-risk AF patients?
- Is the avoidance of long-term warfarin following implantation of the WATCHMAN device associated with a reduced risk of hemorrhagic stroke?
- Is there a signal of a reduced rate cardiovascular or unexplained death in patients treated with the WATCHMAN device?
- Is there a signal of reduced major bleeding complications due the avoidance of long-term use of anticoagulation therapy in patients treated with the WATCHMAN device?

Framing Benefit - Risk

- Is implantation of the WATCHMAN device associated with an acceptable rate of procedure-related complications?
  - Addressed at December 2013 Panel meeting
  - Third primary endpoint (procedural safety) met
  - New operators able to implant the device successfully and safely
- Does the WATCHMAN device provide adequate protection from ischemic stroke or systemic embolism in at-risk AF patients?
- Is the avoidance of long-term warfarin following implantation of the WATCHMAN device associated with a reduced risk of hemorrhagic stroke?
- Is there a signal of a reduced rate cardiovascular or unexplained death in patients treated with the WATCHMAN device?
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Framing Benefit - Risk

- Is implantation of the WATCHMAN device associated with an acceptable rate of procedure-related complications?
- Does the WATCHMAN device provide adequate protection from ischemic stroke or systemic embolism in at-risk AF patients?
- Is the avoidance of long-term warfarin following implantation of the WATCHMAN device associated with a reduced risk of hemorrhagic stroke?
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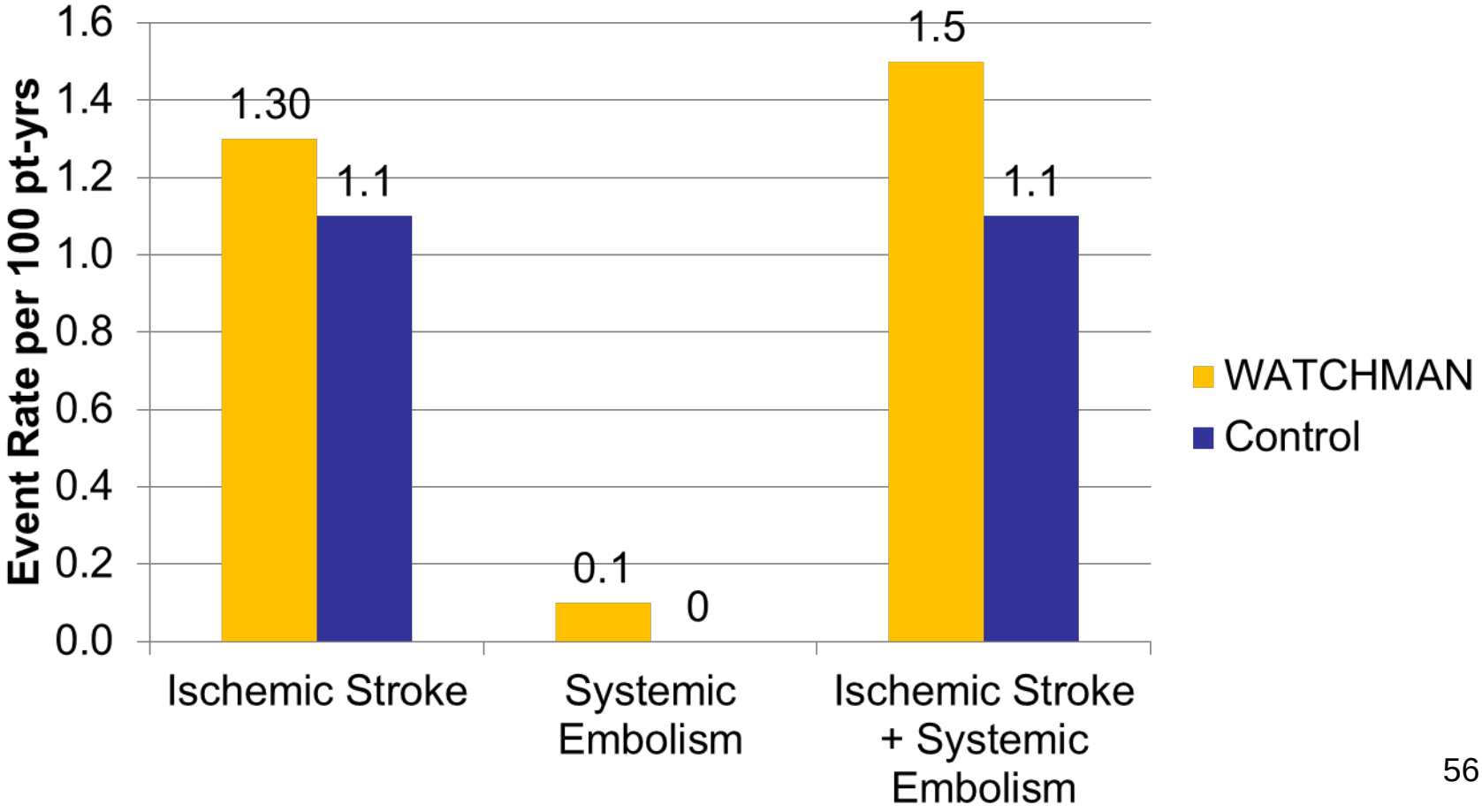
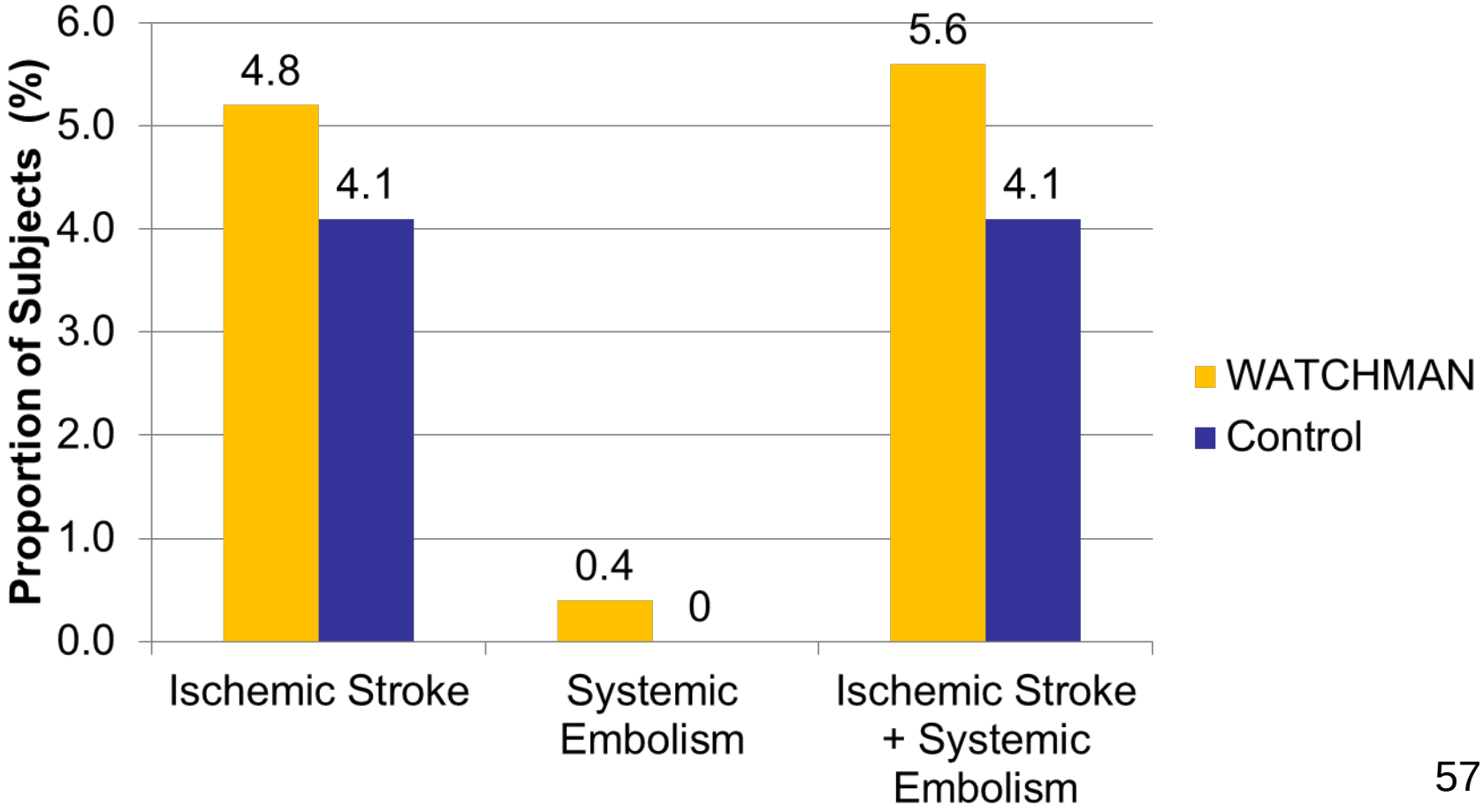
PROTECT AF
Ischemic Stroke or Systemic Embolism

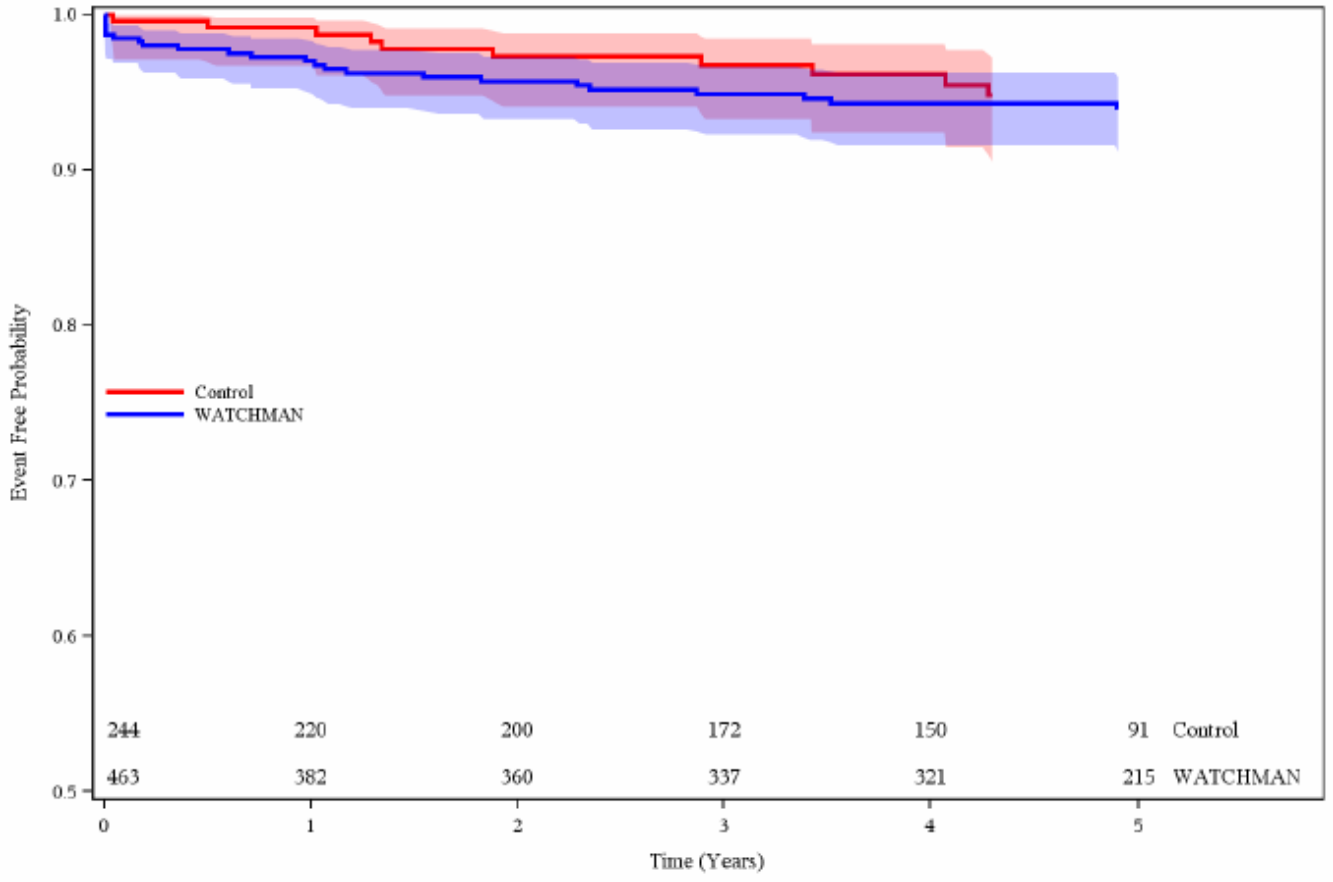


PROTECT AF
Ischemic Stroke or Systemic Embolism

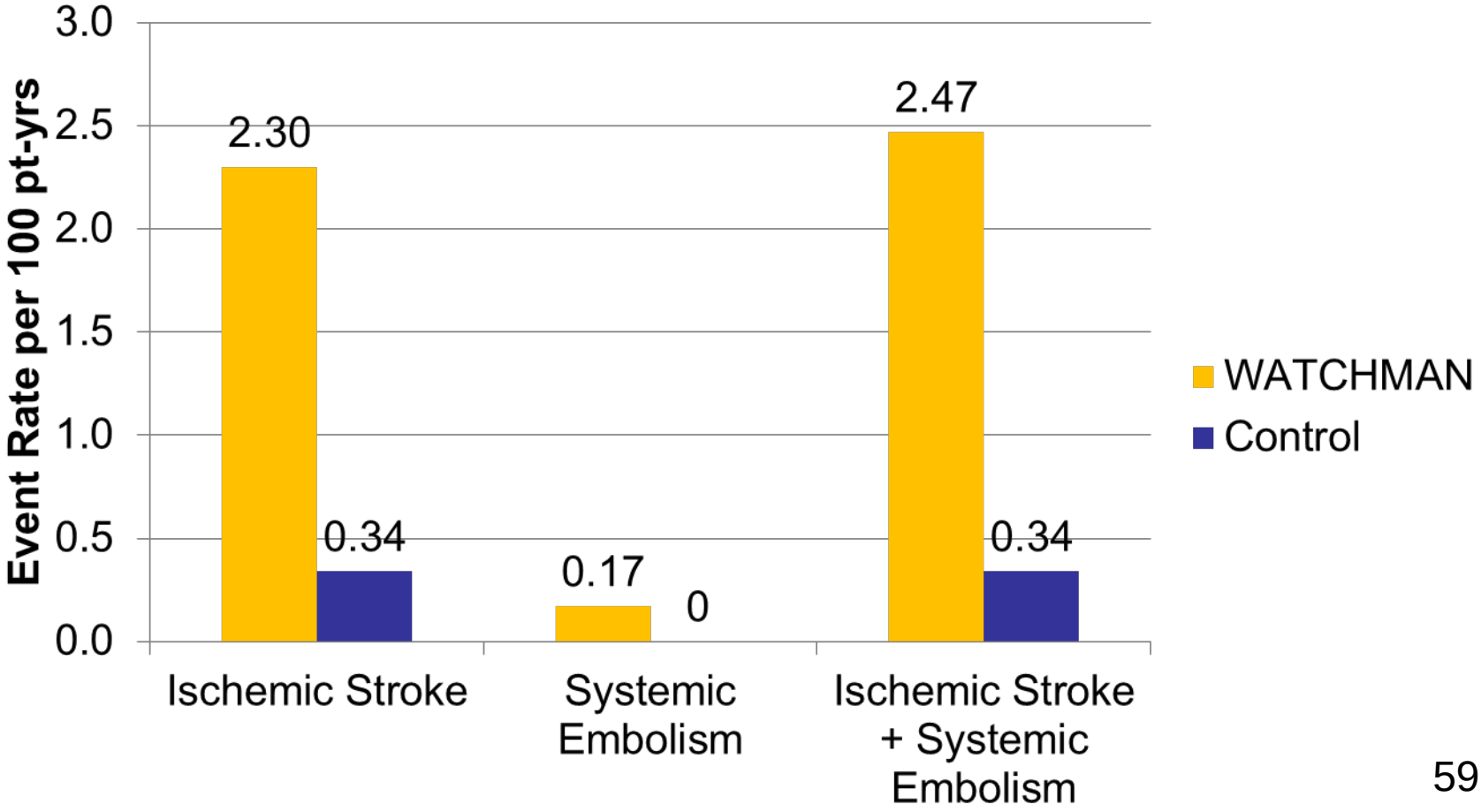


PROTECT AF

Freedom from Ischemic Stroke or Systemic Embolism



PREVAIL Only
Ischemic Stroke or Systemic Embolism



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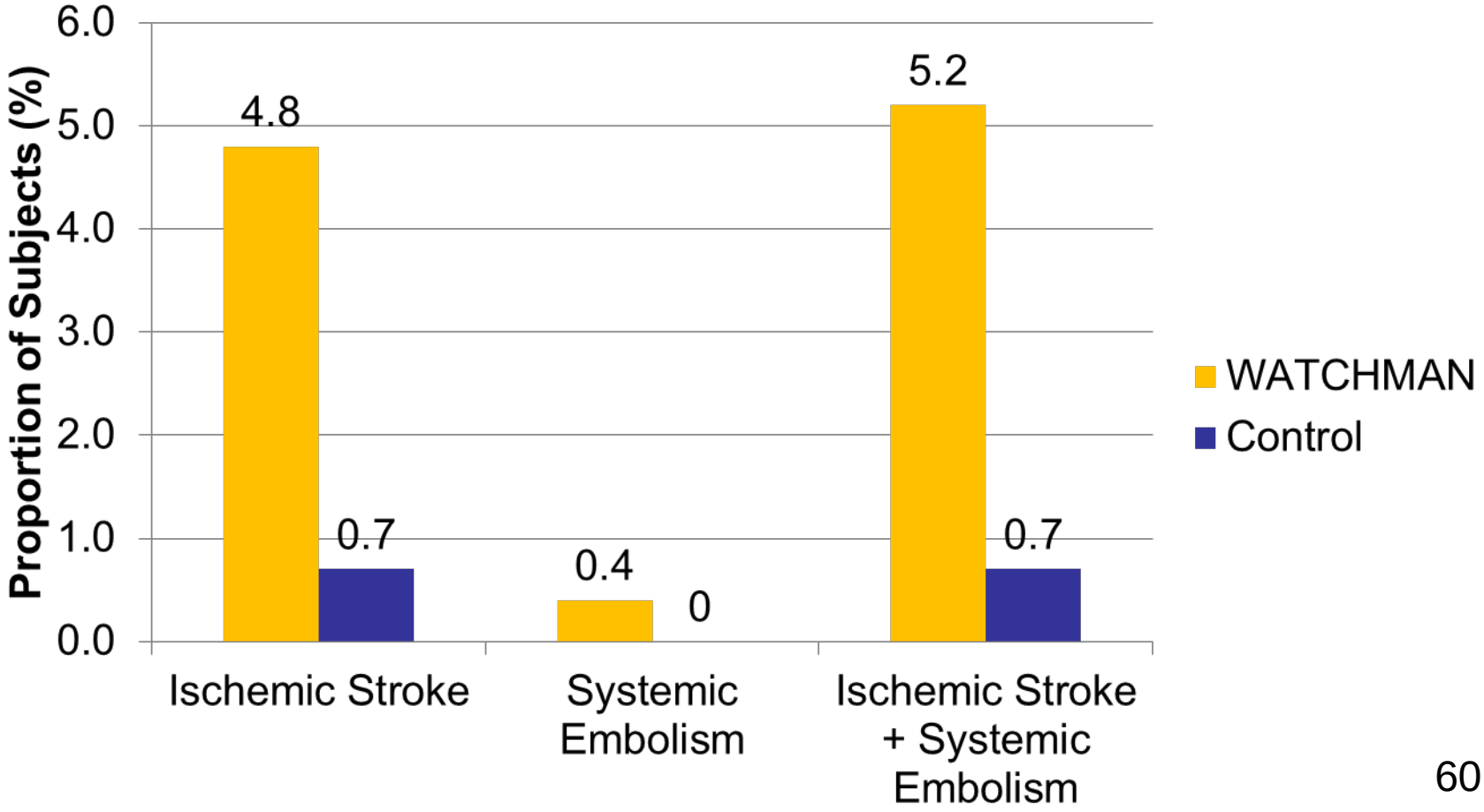
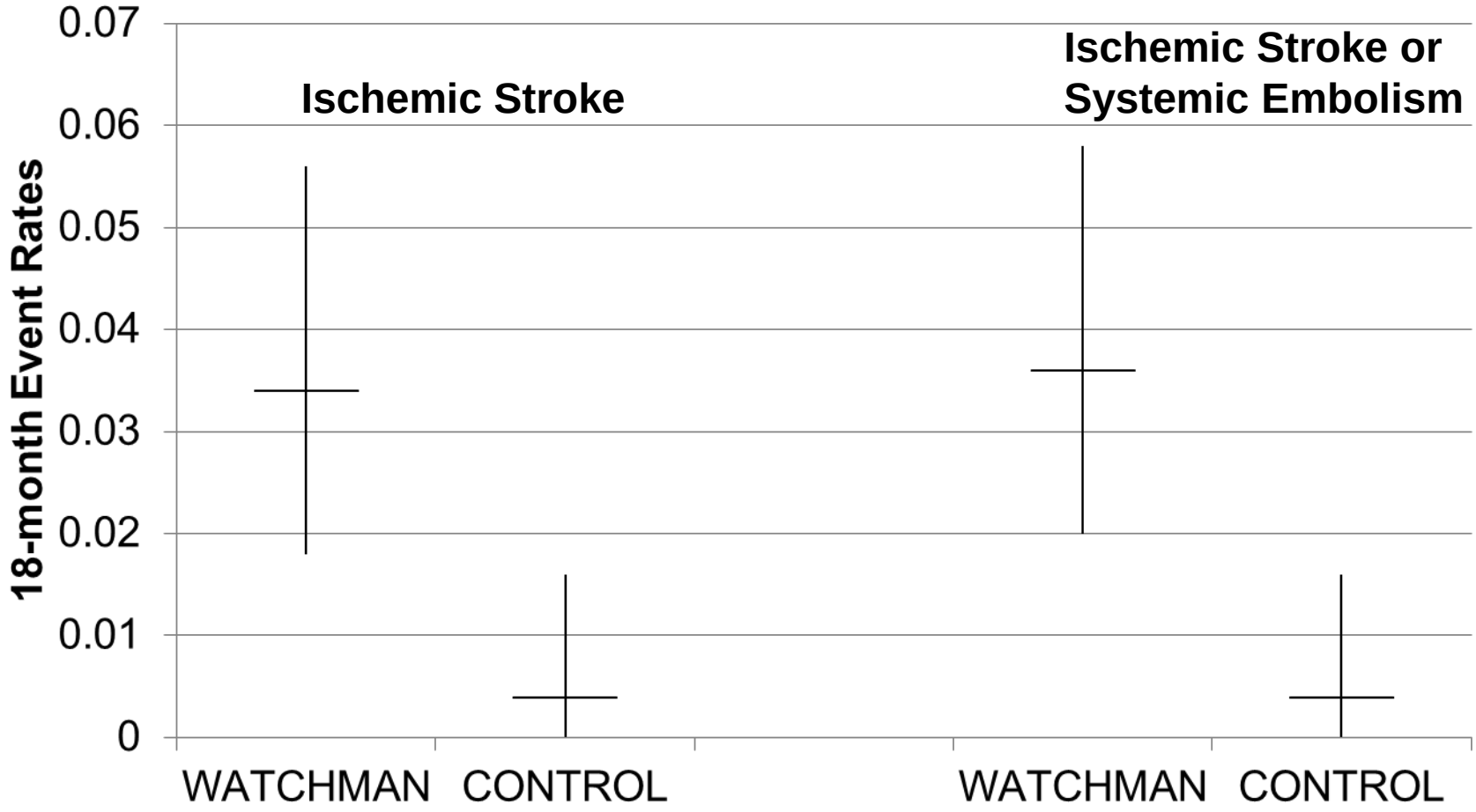


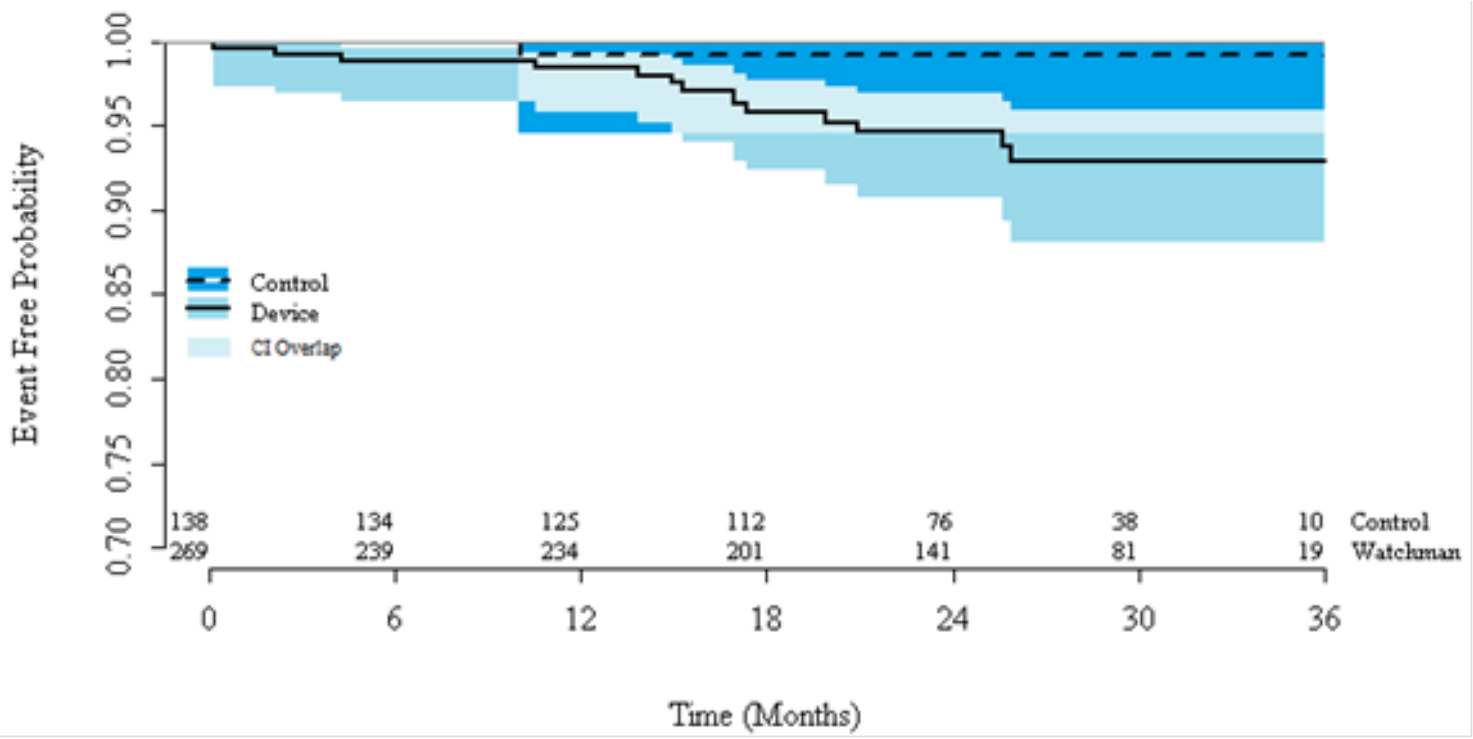
PREVAIL Only

Bayesian Model With a Non-Informative Prior (FDA Analysis)



PREVAIL Only

Freedom from Ischemic Stroke or Systemic Embolism



Log-rank test p-value = 0.03

PREVAIL Second Primary Endpoint

Ischemic Stroke or Systemic Embolism
Occurring After the First 7 Days Post-Randomization

18 month rate Bayesian analysis: Rate difference

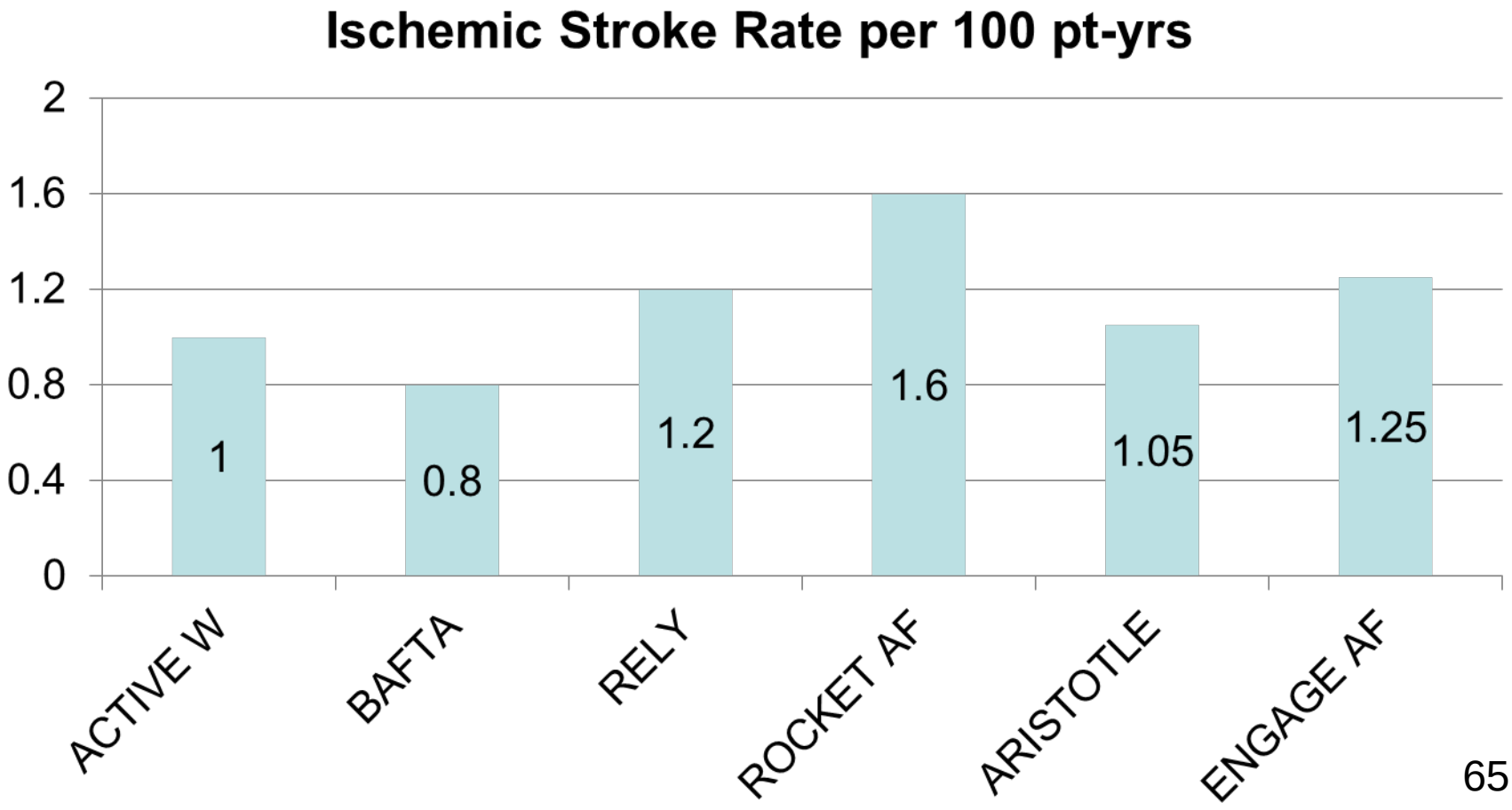
	18 Month Rate				Rate Difference NI Criteria 95% CrI <0.0275
Dataset	**Watchman**	**Control**	**Rate Difference**	**95% CrI**	**NI Criteria Met?**
Jun 2014	0.0294	0.0131	0.0163	-0.0023-0.0342	**No**

CrI = Credible interval, NI = Non-inferiority

Over-Performance of the PREVAIL Only Warfarin Control Group?

Contemporary Anticoagulation Trials

Warfarin Treatment Groups



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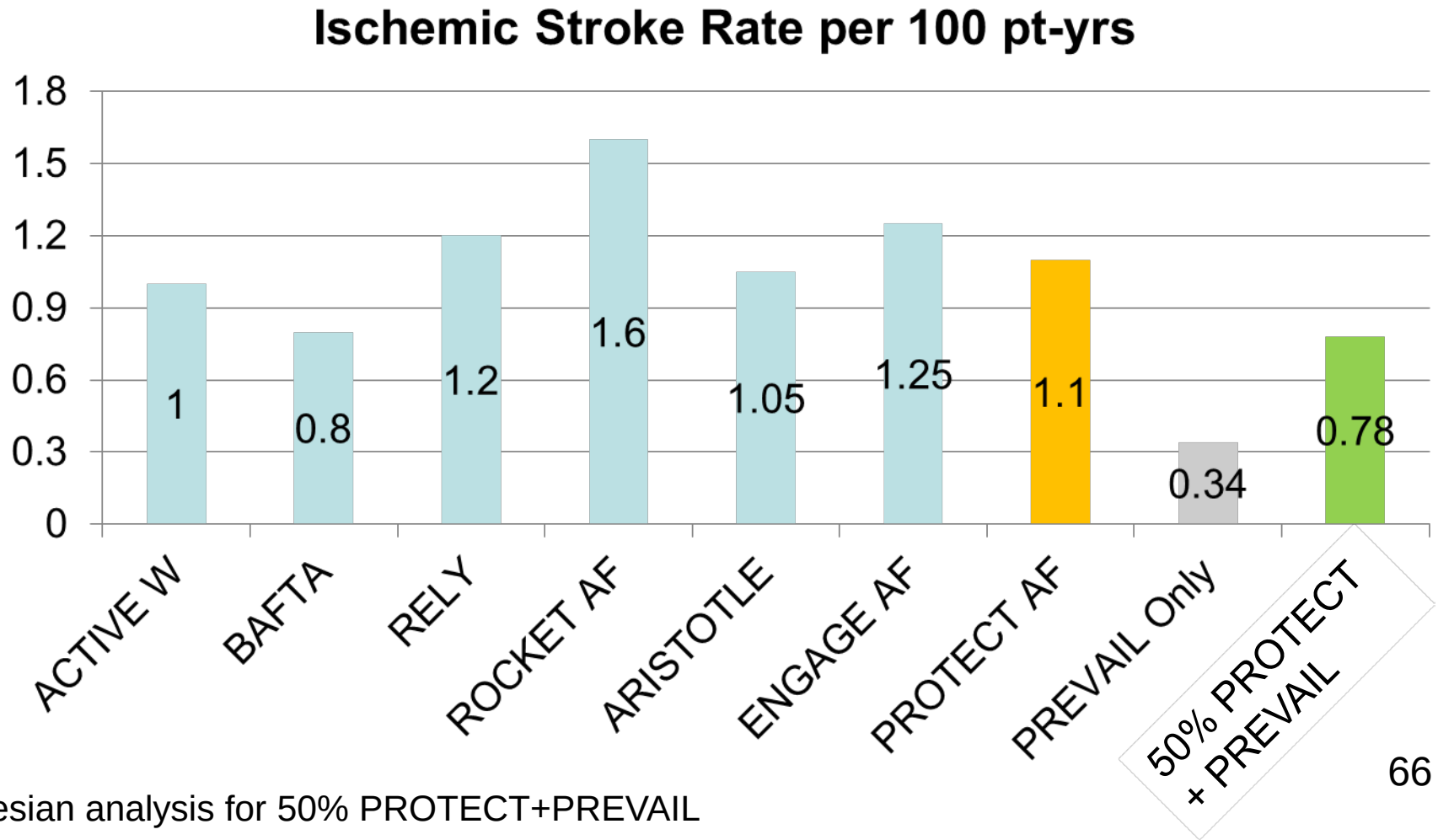
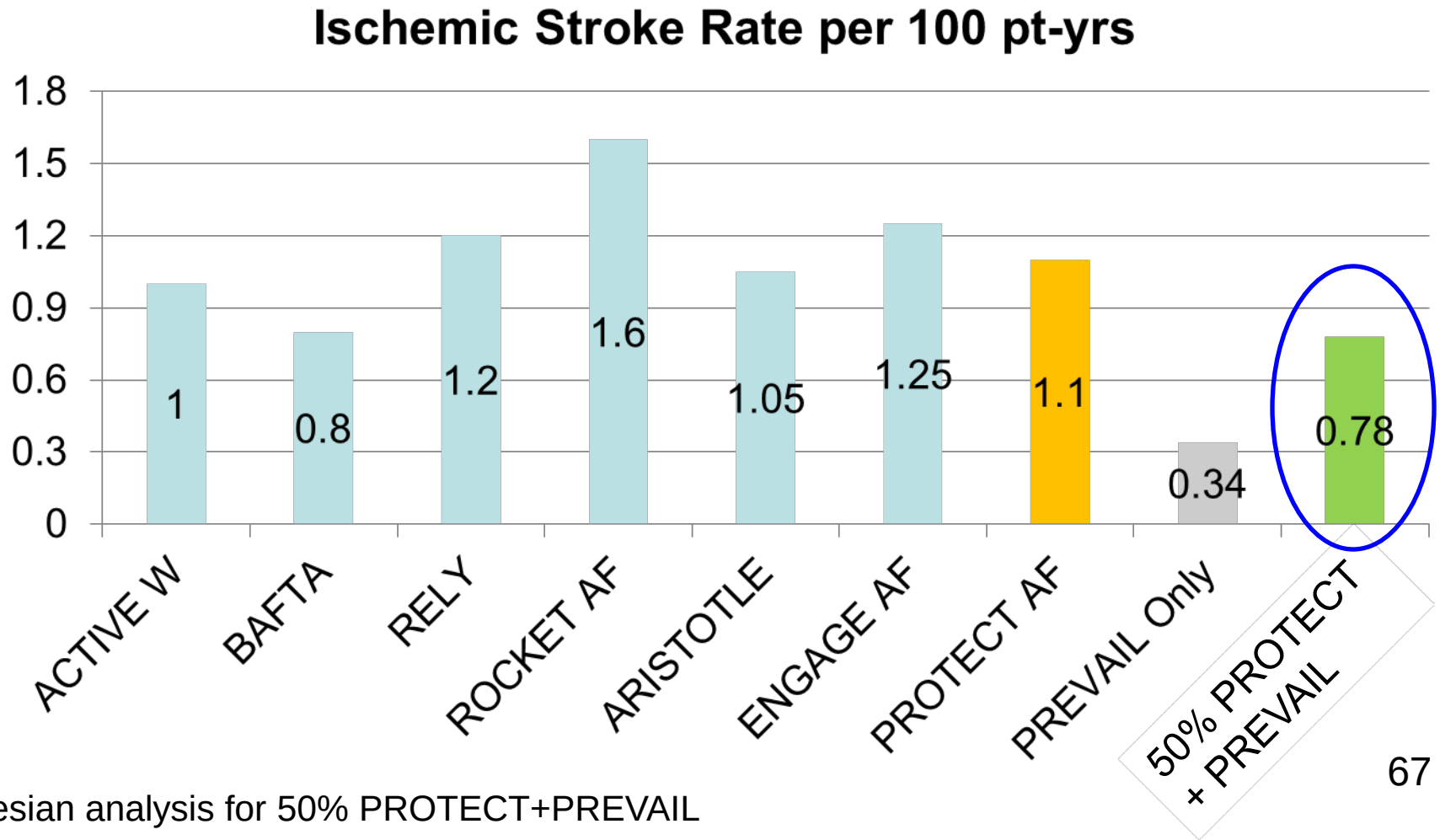
Warfarin Treatment Groups



Bayesian analysis for 50% PROTECT+PREVAIL

Contemporary Anticoagulation Trials

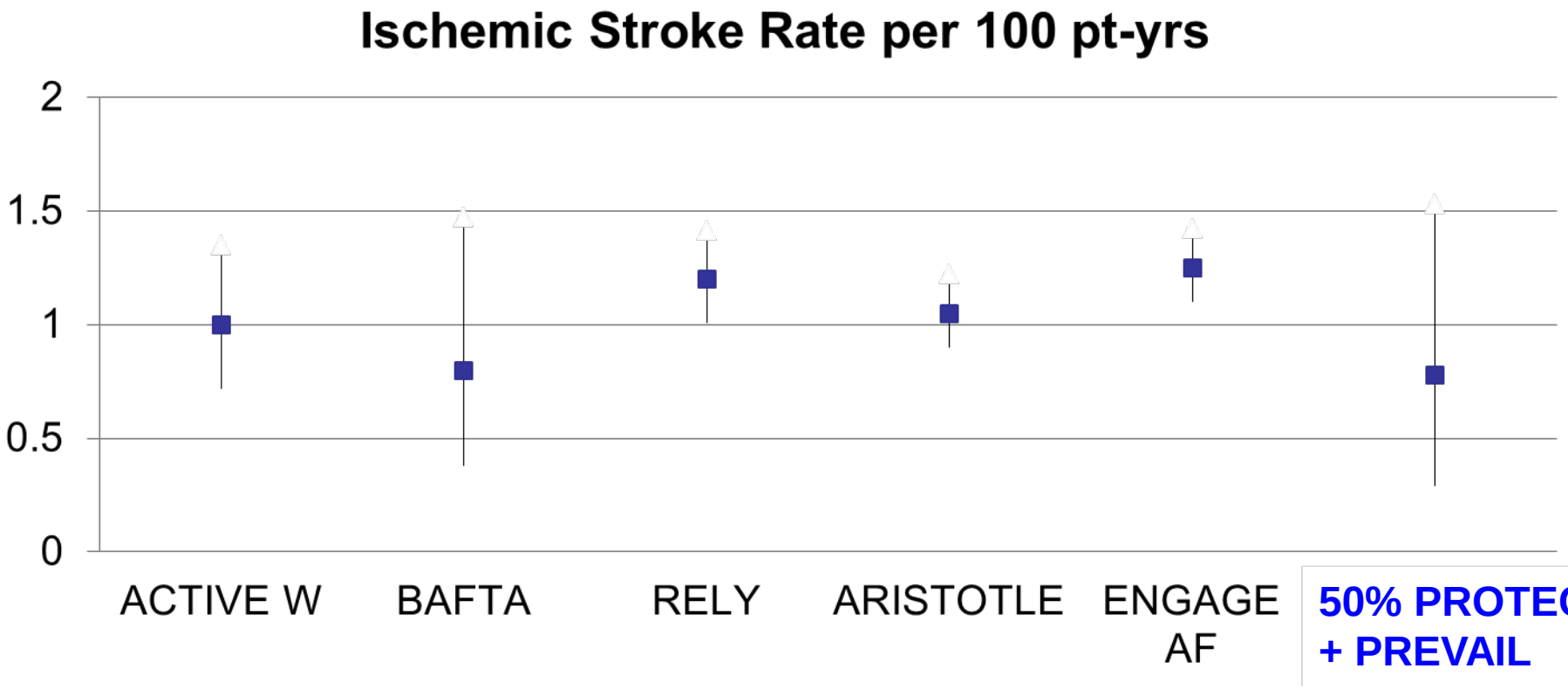
Warfarin Treatment Groups



Bayesian analysis for 50% PROTECT+PREVAIL

Contemporary Anticoagulation Trials

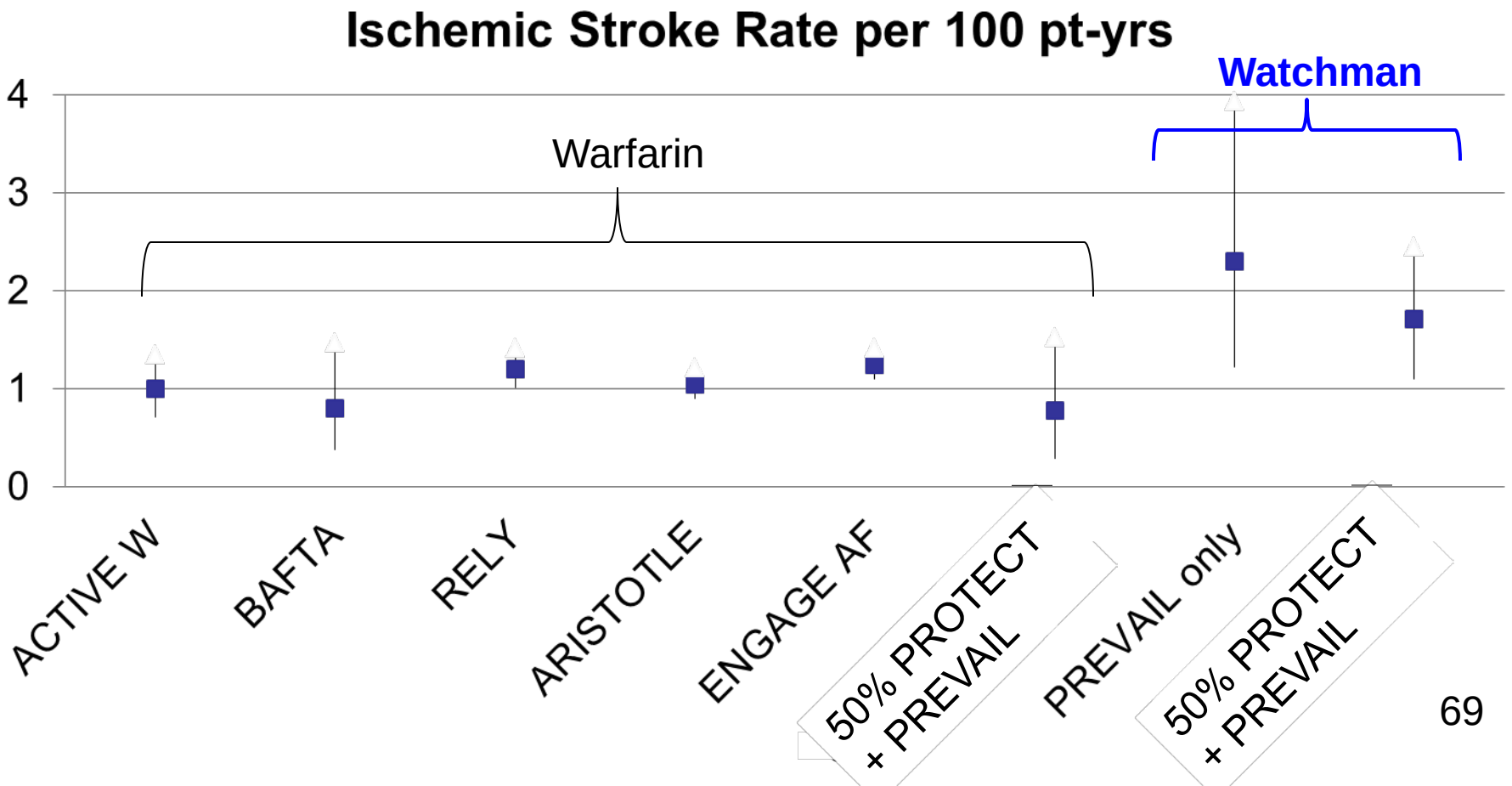
Warfarin Treatment Groups



Bayesian analysis for 50% PROTECT+PREVAIL

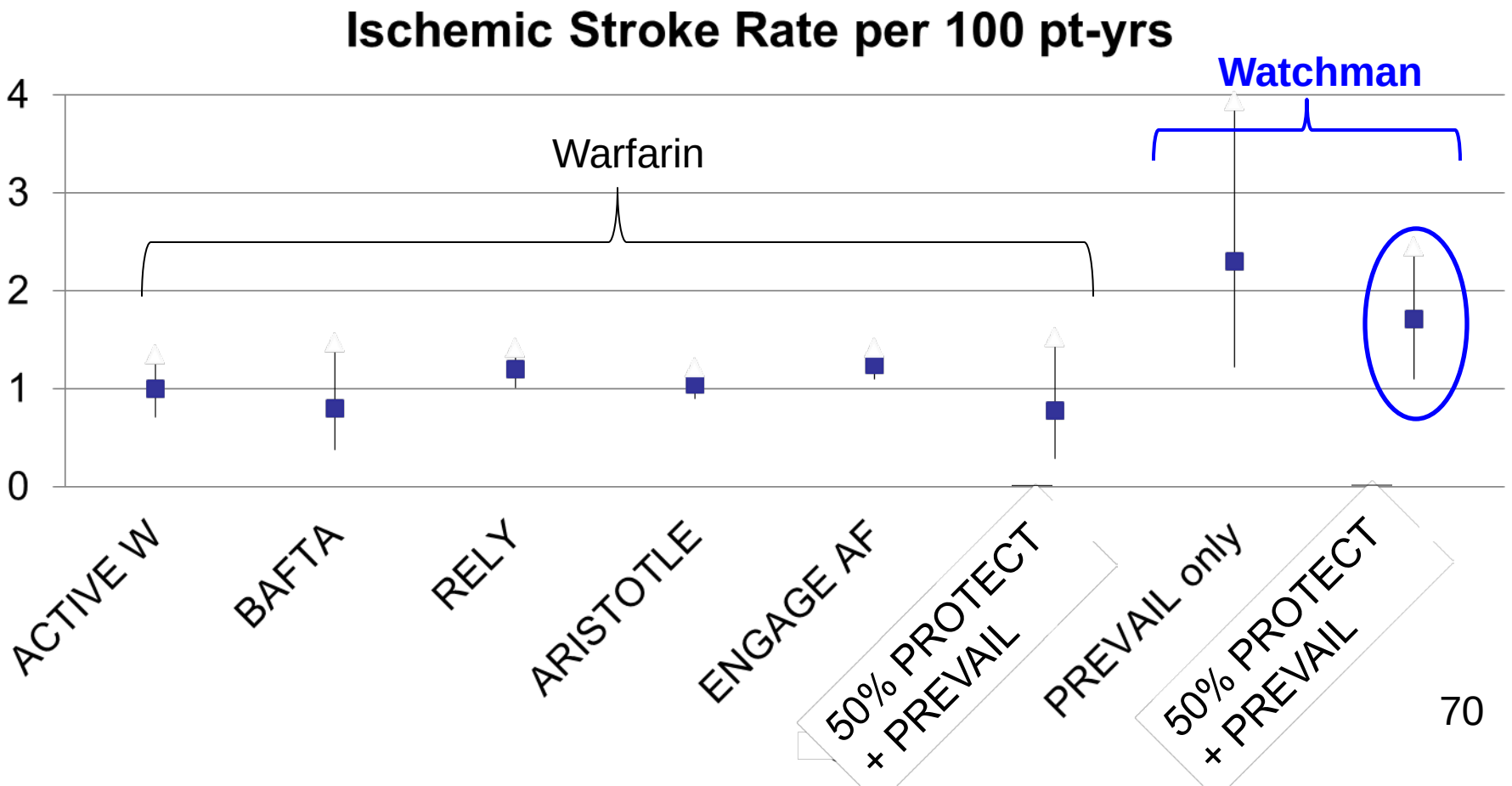
Contemporary Anticoagulation Trials

Warfarin Treatment Groups vs. Watchman



Contemporary Anticoagulation Trials

Warfarin Treatment Groups vs. Watchman



Performance of the PREVAIL Only Warfarin Control Group?

- Reasons for the lower than expected ischemic stroke rate not apparent
- PREVAIL was a well-monitored, well-executed randomized trial
  - Possible that enhanced anticoagulation management (INR control) and management of other risk factors such as HTN and lipids contributed to the low ischemic stroke rate
- Consider the second primary endpoint results in PREVAIL (non-inferiority not met), which included the agreed-upon portion of PROTECT data in the analysis

Does the WATCHMAN device provide adequate protection from ischemic stroke or systemic embolism in at risk AF patients?

- With an additional 18 months of follow-up, the rate of ischemic stroke or systemic embolism strongly favored the Control group in PREVAIL Only
- The rate of ischemic stroke or systemic embolism numerically favored the Control group in PROTECT AF
- In the PREVAIL Bayesian analysis, the WATCHMAN device did not meet non-inferiority for the second primary endpoint of ischemic stroke or systemic embolism occurring >7 days post-procedure

Framing Benefit - Risk

- Is implantation of the WATCHMAN device associated with an acceptable rate of procedure-related complications?
- Does the WATCHMAN device provide adequate protection from ischemic stroke or systemic embolism in at-risk AF patients?
- Is the avoidance of long-term warfarin following implantation of the WATCHMAN device associated with a reduced risk of hemorrhagic stroke?
- Is there a signal of a reduced rate cardiovascular or unexplained death in patients treated with the WATCHMAN device?
- Is there a signal of reduced major bleeding complications due the avoidance of long-term use of anticoagulation therapy in patients treated with the WATCHMAN device?

Does the WATCHMAN Device Reduce the Risk of Hemorrhagic Stroke?

	WATCHMAN	Control
PROTECT AF	3 Events/463 Subjects Rate per 100 pt-yrs = 0.2 (CI 0.03 - 0.48)*	10 Events/244 Subjects Rate per 100 pt-yrs = 1.1 (CI 0.52 - 2.00)
PREVAIL-Only	2 Events/269 Subjects Rate per 100 pt-yrs = 0.35 (CI 0.04 - 1.25)	2 Events/138 Subjects Rate per 100 pt-yrs = 0.67 (CI - 0.08, 2.41)

2:1 Randomization WATCHMAN:Control
*95% CI calculations performed assuming Poisson distribution

Does the WATCHMAN Device Reduce the Risk of Hemorrhagic Stroke?

Focus on PROTECT AF

PROTECT AF	WATCHMAN 463 Randomized Subjects	Control 244 Randomized Subjects
Hemorrhagic Stroke Events	3	10
Rate per 100 pt-yrs	0.2	1.1
% of Randomized Subjects	0.6%	4.1%

Does the WATCHMAN Device Reduce the Risk of Hemorrhagic Stroke?

Focus on the PROTECT AF Warfarin Control Group

PROTECT AF	WATCHMAN 463 Randomized Subjects	Control 244 Randomized Subjects
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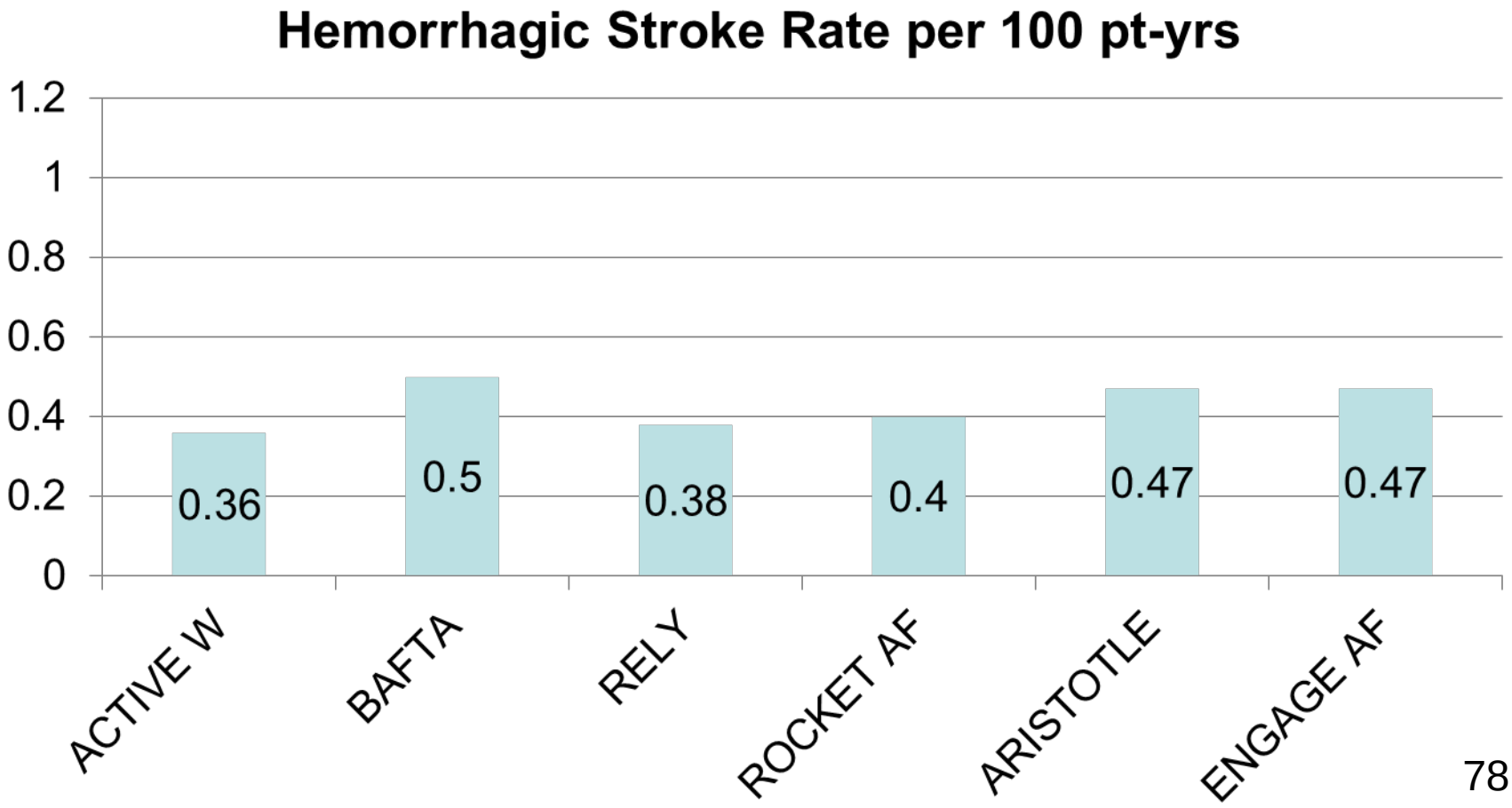
Is the signal of benefit robust?

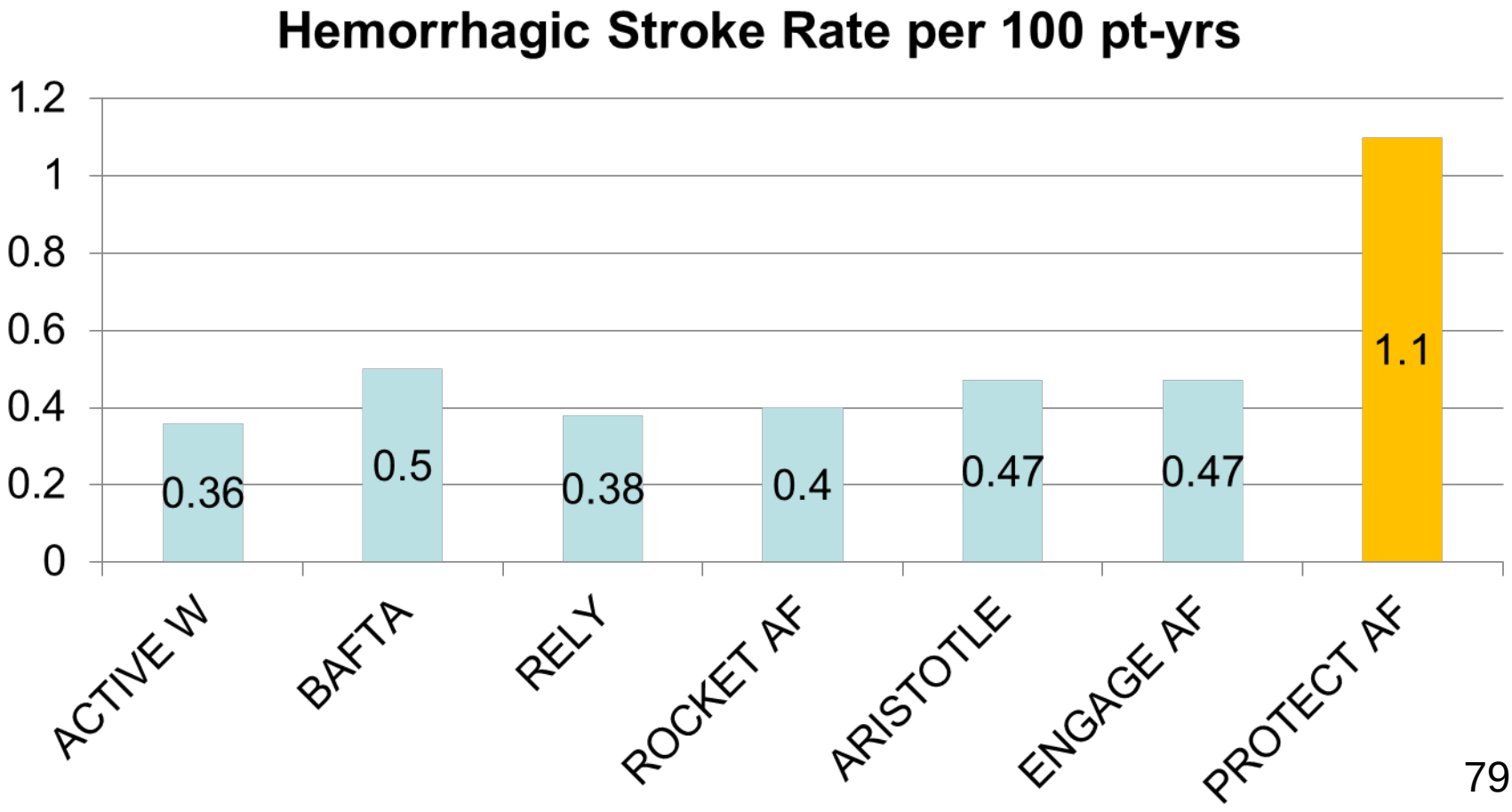
Contemporary Anticoagulation Trials

Warfarin Treatment Groups



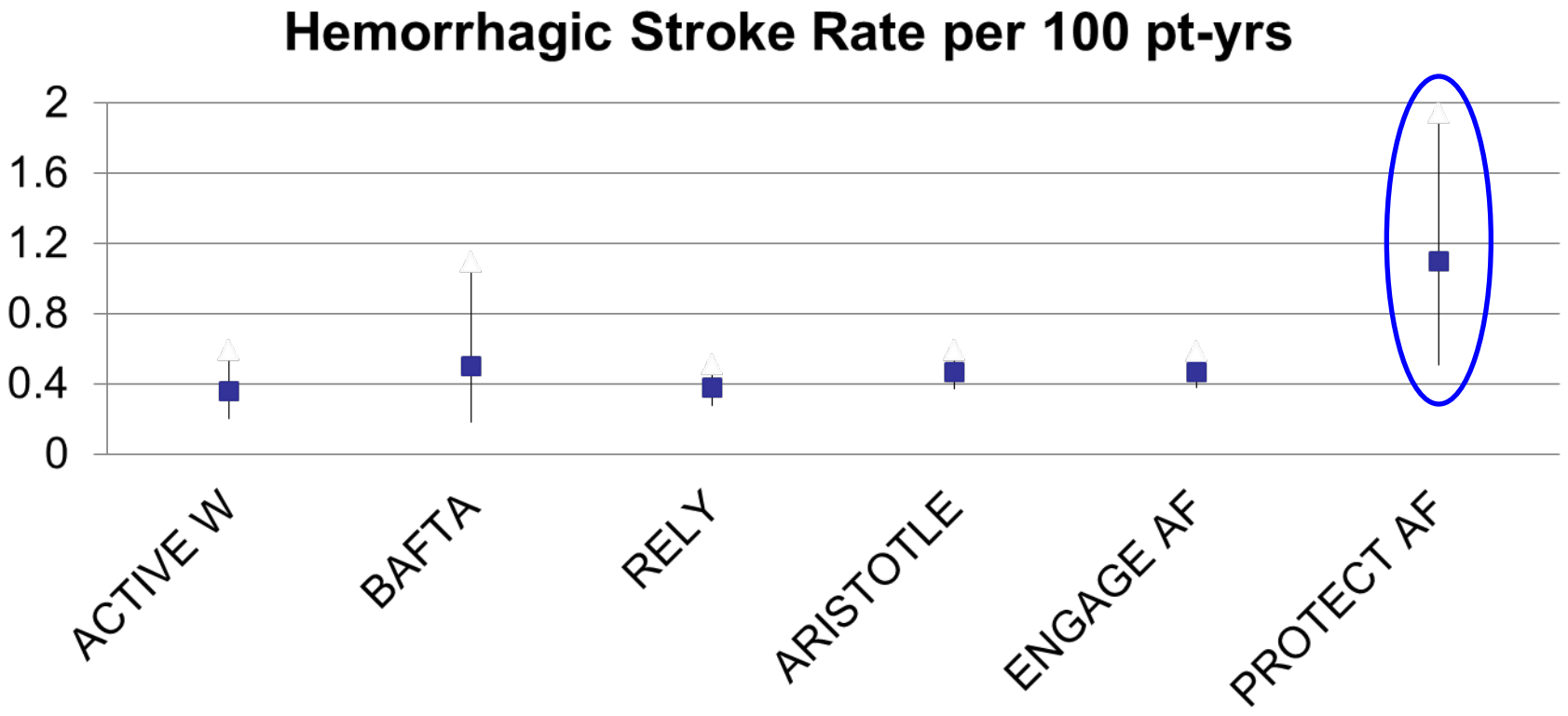
Contemporary Anticoagulation Trials

Warfarin Treatment Groups



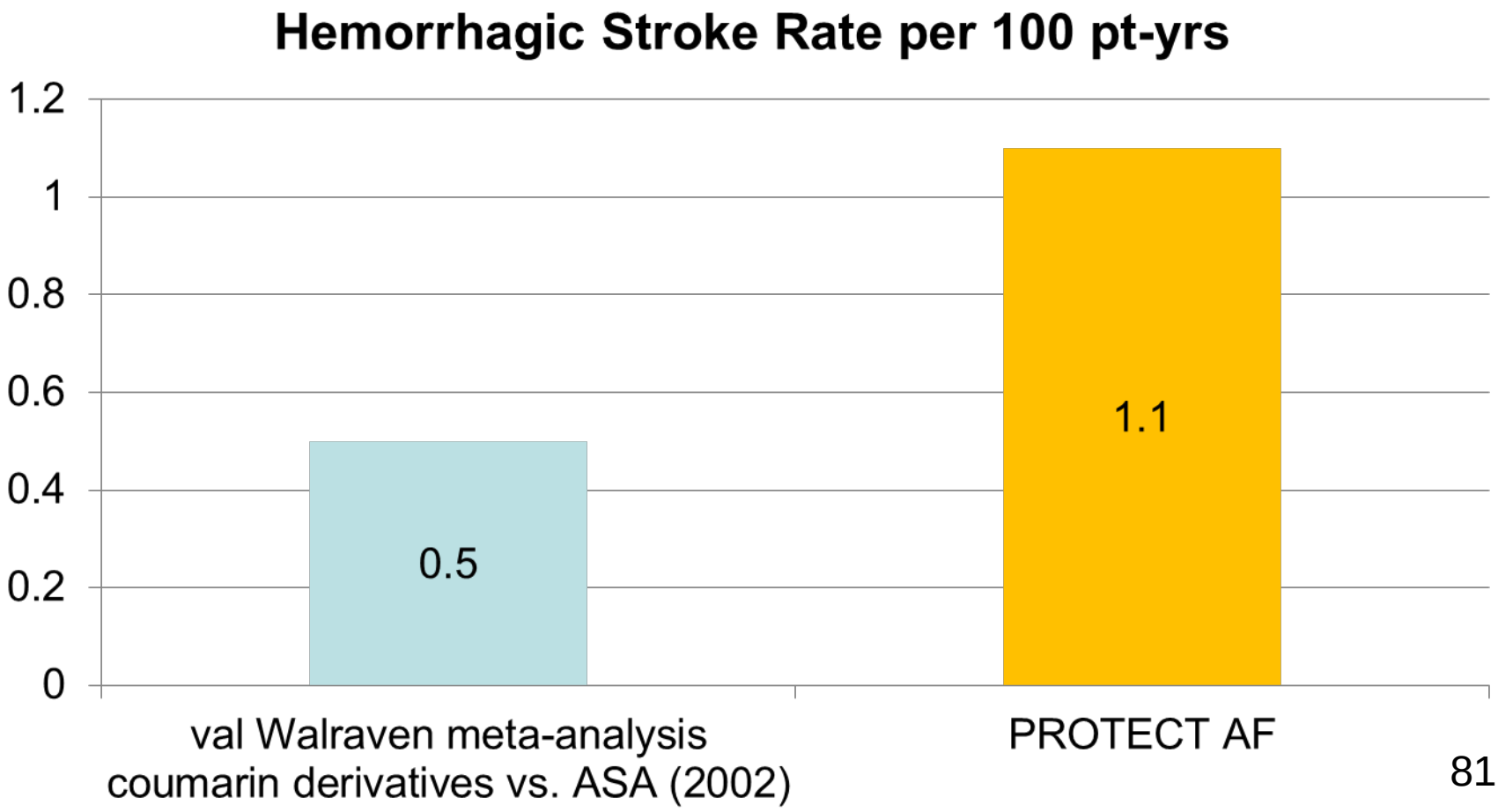
Contemporary Anticoagulation Trials

Warfarin Treatment Groups



Anticoagulation Trials

Warfarin Treatment Groups



Hemorrhagic Stroke
PROTECT AF Warfarin Control Group

- 10 hemorrhagic stroke events in Control group; however:
  - 1 subject off warfarin for >38 months at the time of the event (taking ASA alone)
  - 1 subject had no CNS imaging performed
    - Protocol definition of hemorrhagic stroke requires CT or MRI confirmation

Hemorrhagic Stroke
PROTECT AF Warfarin Control Group

- 10 hemorrhagic stroke (HS) events in Control group; however:
  - 4 subjects were taking ASA at the time of the HS
  - Antiplatelet use information not available for 1 subject
  - Professional society guidelines on use of ASA
    - 2006 ACC/AHA/ECS: The addition of ASA to anticoagulation in stable vascular disease patients offers no benefit and increases the bleeding risk (including intracranial hemorrhage)
    - 2010 ESC: Concomitant antiplatelet therapy should not be prescribed in the absence of a subsequent cardiovascular event (ECS 2010)

Hemorrhagic Stroke and Cranial Bleeds

PROTECT AF Warfarin and WATCHMAN Groups

- 10 hemorrhagic stroke (HS) events in Control group; however:
  - 5 events adjudicated as HS occurred following falls
    - 4 associated with subdural hematomas (one of which also had intracerebral bleeding in subject on ASA alone), and 1 SAH
    - 2 subjects hit their head, 1 fell down steps, and information lacking on the other 2
    - Concomitant use of antiplatelet agents in at least 2 of the 4 subjects taking warfarin
- 3 WATCHMAN subjects fell resulting in subdural hematomas
  - 2 on ASA alone and 1 on aspirin plus warfarin,
  - These cases were *not* adjudicated as HS

Hemorrhagic Stroke and Cranial Bleeds

PROTECT AF Warfarin and WATCHMAN Groups

PROTECT AF	WATCHMAN 463 Randomized Subjects	Control 244 Randomized Subjects
Hemorrhagic Stroke (HS) Events	3	10
Non-Hemorrhagic Stroke Intracranial Bleeding (Non-HS) Events	5	1
HS + Non-HS Events	**8**	**11**
% of Randomized Subjects	1.7%	4.5%

2:1 Randomization WATCHMAN:Control

Is the PROTECT AF Hemorrhagic Stroke (HS) Reduction Robust?

	WATCHMAN	Control
Hemorrhagic Stroke Events	3/463 Subjects	10/244 Subjects
Rate per 100 pt-yrs	0.2	1.1

- Control group HS rate >2-fold higher than reported in other contemporary oral anticoagulation trials
- Non-use of warfarin in 1 subject and no CNS imaging in 1 subject
- Concomitant use of antiplatelet agents
- Adjudication challenges with cranial bleeds associated with head trauma (falls)
- Signal of a reduced HS risk in WATCHMAN subjects vs. Control not observed in the PREVAIL Only dataset

Framing Benefit - Risk

- Is implantation of the WATCHMAN device associated with an acceptable rate of procedure-related complications?
- Does the WATCHMAN device provide adequate protection from ischemic stroke or systemic embolism in at-risk AF patients?
- Is the avoidance of long-term warfarin following implantation of the WATCHMAN device associated with a reduced risk of hemorrhagic stroke?
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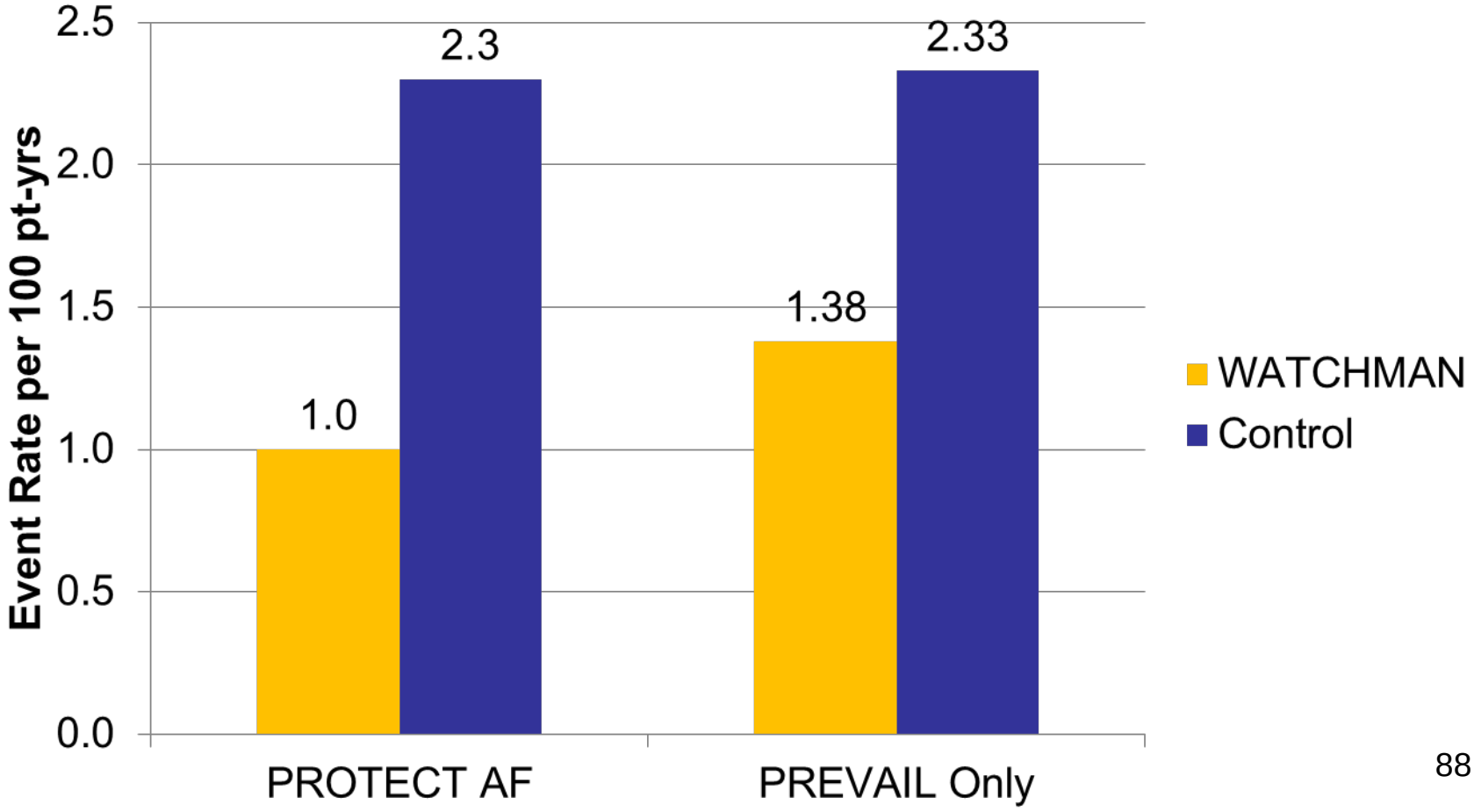
Cardiovascular and Unexplained Deaths PROTECT AF and PREVAIL Only



Cardiovascular Risk Factors: PROTECT + PREVAIL

	WATCHMAN, N=732	Control, N=382	P-value
Age (PROT/PREV)	72/74 yrs	73/75 yrs	NS
CAD	44%	50%	NS
MI	14%	20%	0.013
CABG	24%	27%	NS
Coronary Intervention	25%	28%	NS
CHF (PREV)	23%	23%	NS
ICD or PPM (PREV)	28%	37.7%	NS
PAD	11%	11%	NS
Stroke (PREV)	22%	21%	NS
Current Smoker	5%	6%	NS
Former Smoker	43%	47%	NS
HTN	89%	93%	NS
Hyperlipidemia	64%	70%	NS
Diabetes (PREV)	34%	30%	NS

Cardiovascular Risk Factors: PROTECT + PREVAIL

	WATCHMAN, N=732	Control, N=382	P-value
Age (PROT/PREV)	**72/74 yrs**	**73/75 yrs**	NS
CAD	**44%**	**50%**	NS
MI	14%	20%	0.013
CABG	24%	27%	NS
Coronary Intervention	25%	28%	NS
CHF (PREV)	23%	23%	NS
ICD or PPM (PREV)	28%	38%	NS
PAD	11%	11%	NS
Stroke (PREV)	22%	21%	NS
Current Smoker	5%	6%	NS
Former Smoker	43%	47%	NS
HTN	**89%**	**93%**	NS
Hyperlipidemia	**64%**	**70%**	NS
Diabetes (PREV)	34%	30%	NS

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Mode of Cardiovascular or Unexplained Death PROTECT AF

	CV/Unexplained Death					
	N	Sudden Cardiac Death*	Unexplained/ Other	MI	Heart Failure	Stroke or Cranial Bleed
WATCHMAN 463 Subjects	19	10	0	1	5	5
Control 244 Subjects	22	6	3	4	3	6

*Relevant co-morbidities among subjects with sudden cardiac death include age, CAD, prior MI, left ventricular dysfunction, heart failure, ICD, AV and MV disease

Mode of Cardiovascular or Unexplained Death PREVAIL Only

	CV/Unexplained Death			
	Sudden Cardiac Death*	**Acute MI**	**Heart Failure**	**Stroke or Cranial Bleed**
WATCHMAN 269 Subjects	6	2	0	2
Control 138 Subjects	5	0	1	2

*Relevant co-morbidities among subjects with sudden cardiac death include age, HTN, diabetes, CAD, prior MI, left ventricular dysfunction, heart failure

Is the signal of a reduced rate cardiovascular or unexplained death attributable to the WATCHMAN device?

- Fatal non-stroke and non-cranial bleeding events are counted toward the primary endpoints of PROTECT AF and PREVAIL but were not causally associated with:
  - Warfarin use in the Control group; or
  - The WATCHMAN device or implant procedure
- Mortality rate differences that include stroke-related deaths favor the WATCHMAN group in PROTECT AF, but the difference is driven by events adjudicated as hemorrhagic strokes

Framing Benefit - Risk

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- Does the WATCHMAN device provide adequate protection from ischemic stroke or systemic embolism in at-risk AF patients?
- Is the avoidance of long-term warfarin following implantation of the WATCHMAN device associated with a reduced risk of hemorrhagic stroke?
- Is there a signal of a reduced rate cardiovascular or unexplained death in patients treated with the WATCHMAN device?
- Is there a signal of reduced major bleeding complications due the avoidance of long-term use of anticoagulation therapy in patients treated with the WATCHMAN device?

Major Bleeding

- Reduction in the rate of bleeding complications associated with the use or anticoagulants is a potential advantage of the WATCHMAN device
- In the WATCHMAN trials, major bleeding was defined as events adjudicated as serious adverse events,
  - An objective bleeding scale such as the GUSTO or TIMI was not used

PROTECT AF Major Bleeding

	WATCHMAN		Control	
	N Events/ Subjects (%)	**Rate (N Events/ Total Pt-Yrs)**	**N Events/ Subjects (%)**	**Rate (N Events/ Total Pt-Yrs)**
Procedure-related	28/463 (6.0%)	NA	NA	NA
Non-procedure related	24/463 (5.2%)	1.3 (24/1803.7)	29/244 (11.9%)	3.2 (29/904.9)
0 - 45 days	5/463 (1.1%)	9.2 (5/54.6)	2/244 (0.8%)	6.7 (2/29.7)
45 days – 6 months	4/431 (0.9%)	2.6 (4/153.6)	4/239 (1.7%)	4.6 (4/87.8)
>6 months	15/397 (3.8%)	0.9 (15/1595.5)	23/228 (10.1%)	2.9(23/787.5)
Total major bleeding	50/463 (10.8%)	2.9 (50/1743.4)	29/244 (11.9%)	3.2 (29/904.9)

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PREVAIL Only Major Bleeding

	WATCHMAN		Control	
	N Events/ Subjects (%)	**Rate (N Events/ Total Pt-Yrs)**	**N Events/ Subjects (%)**	**Rate (N Events/ Total Pt-Yrs)**
Procedure-related	12/269 (4.5%)	NA	NA	NA
Non-procedure related	20/269 (7.4%)	3.6 (20/550.1)	14/138 (10.1%)	5.0 (14/282.1)
0 - 45 days	8/269 (3.0%)	25.0 (8/31.9)	0/138 (0.0%)	0.0 (0/16.9)
45 days – 6 months	7/269 (2.6%)	7.9 (7/88.6)	3/138 (2.2%)	6.0 (3/50.4)
>6 months	5/269 (1.9%)	1.2 (5/429.6)	11/138 (8.0%)	5.1 (11/214.8)
Total major bleeding	29/269 (10.8%)	5.5 (29/531.1)	14/138 (10.1%)	5.0 (14/282.1)

PREVAIL Only Major Bleeding

	WATCHMAN		Control	
	N Events/ Subjects (%)	**Rate (N Events/ Total Pt-Yrs)**	**N Events/ Subjects (%)**	**Rate (N Events/ Total Pt-Yrs)**
Procedure-related	12/269 (4.5%)	NA	NA	NA
Non-procedure related	20/269 (7.4%)	3.6 (20/550.1)	14/138 (10.1%)	5.0 (14/282.1)
0 - 45 days	8/269 (3.0%)	25.0 (8/31.9)	0/138 (0.0%)	0.0 (0/16.9)
45 days – 6 months	7/269 (2.6%)	7.9 (7/88.6)	3/138 (2.2%)	6.0 (3/50.4)
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Total major bleeding	29/269 (10.8%)	5.5 (29/531.1)	14/138 (10.1%)	5.0 (14/282.1)

PROTECT AF Control Group Major Bleeding *Non-CNS Related*

- 24 Adjudicated serious adverse bleeding events in 19 subjects
- Narrative review
  - 22 GI bleeds
  - 1 Tracheostomy site bleed
  - 1 Anemia with no site identified
- At least 5 of 19 subjects taking antiplatelet agents in addition to an anticoagulant
  - ASA use/non-use not stated in narrative summaries in 8 additional subjects

PREVAIL Only Control Group Major Bleeding

- 16 Adjudicated serious adverse bleeding events in 15 subjects
- Narrative review
  - 8 GI bleeds
  - 2 Hematuria
  - 2 Epistaxis
  - 4 Other
- 10 of 16 subjects taking ASA in addition to an anticoagulant

Is there a signal of reduced major bleeding complications due the avoidance of long-term use of anticoagulation therapy in patients treated with the WATCHMAN device?

- Neither PROTECT AF nor PREVAIL showed a reduction in overall major bleeding rates between the WATCHMAN and the Control groups
- A signal of a reduced rate of late major bleeding was seen in the WATCHMAN group
  - An expected finding in view of the lower intensity of antithrombotic therapy in WATCHMAN subjects
- Concomitant use of ASA with warfarin may have increased the bleeding risk in the Control group

HAS-BLED vs. $CHADS_2$ Risk Scores

HAS-BLED	
Condition	Points
HTN	1
Abnormal liver or renal function	1 or 2
Stroke	1
Bleeding	1
Labile INR	1
Age >65	1
Drugs or ETOH	1 or 2

HAS-BLED vs. $CHADS_2$ Risk Scores

HAS-BLED	
Condition	Points
HTN	1
Abnormal liver or renal function	1 or 2
Stroke	1
Bleeding	1
Labile INR	1
Age >65	1
Drugs or ETOH	1 or 2

$CHADS_2$	
Condition	Points
Heart Failure	1
HTN	1
Age ≥75	1
Diabetes	1
Stroke or TIA	2

HAS-BLED vs. CHA_2DS_2-VASc Risk Scores

HAS-BLED	
Condition	Points
HTN	1
Abnormal liver or renal function	1 or 2
Stroke	1
Bleeding	1
Labile INR	1
Age >65	1
Drugs or ETOH	1 or 2

CHA_2DS_2-Vc	
Condition	Points
Heart Failure	1
HTN	1
Age ≥75	2
Diabetes	1
Stroke or TIA	2
Vascular Disease	1
Age 65-74	1
Female	1

In considering benefit-risk, patients at high risk for bleeding are often at high risk for stroke

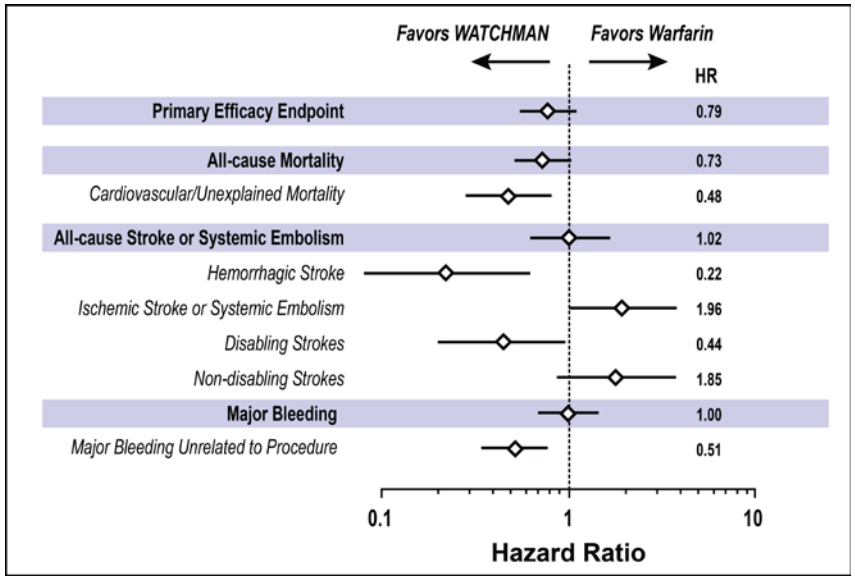
HAS-BLED Risk Scores and the WATCHMAN Studies

- HAS-BLED scores were not prospectively collected in the WATCHMAN studies
  - No sub-group analysis of outcomes stratified by HAS-BLED scores
- There are no studies evaluating the benefit-risk profile of the WATCHMAN device vs. alternative therapies in high HAS-BLED score patients

Benefit – Risk Elements

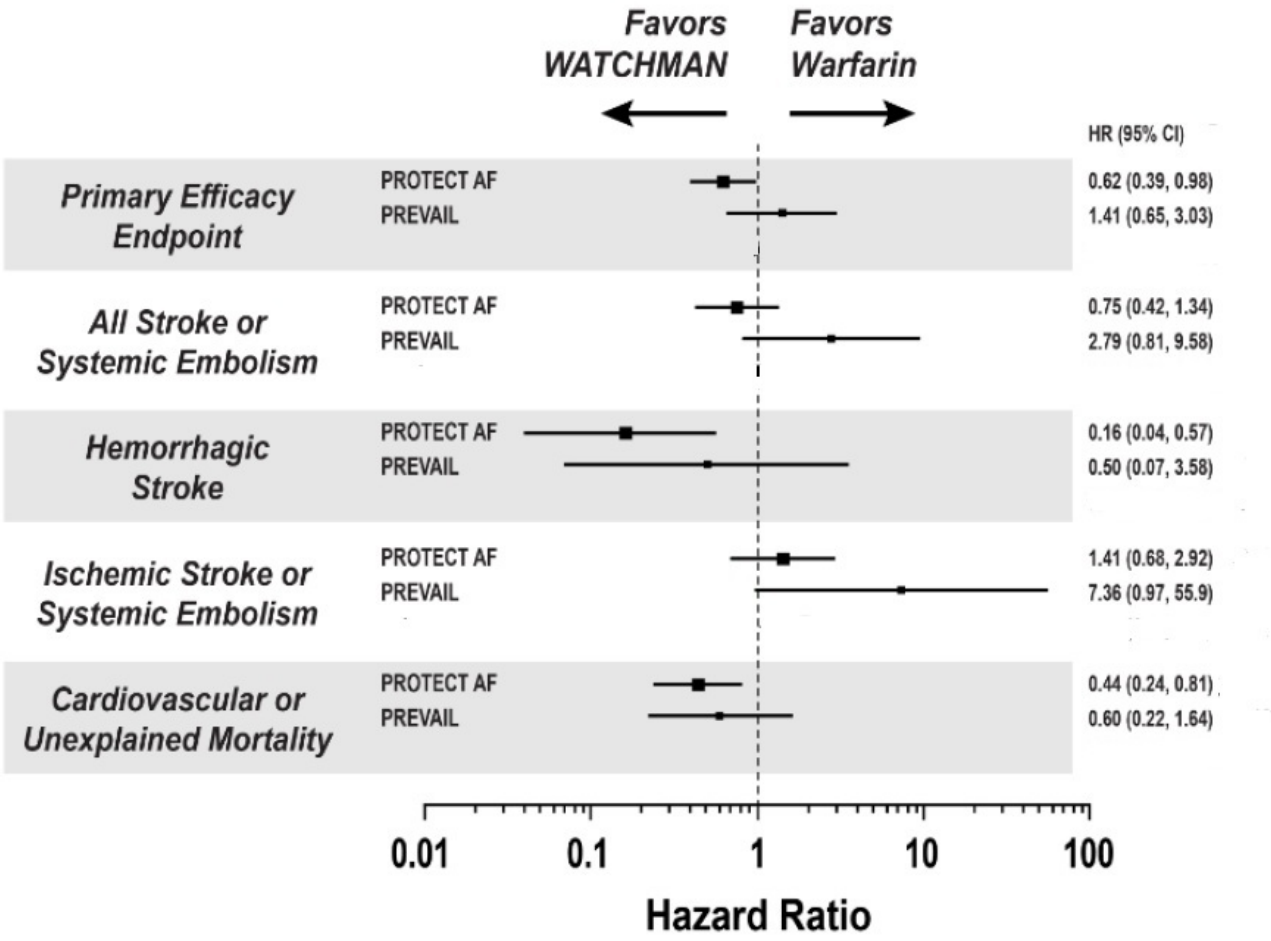
- Does the WATCHMAN device offer:
  - Adequate protection from ischemic stroke or systemic embolism?
  - A reduced risk of hemorrhagic stroke?
  - A reduced rate of cardiovascular or unexplained death?
  - A reduced risk of serious bleeding complications?

Sponsor's Patient Level Meta-Analysis



- Pools results from PROTECT AF and PREVAIL
- Does pooling provide a completely accurate picture of benefit-risk?

PROTECT AF vs. PREVAIL



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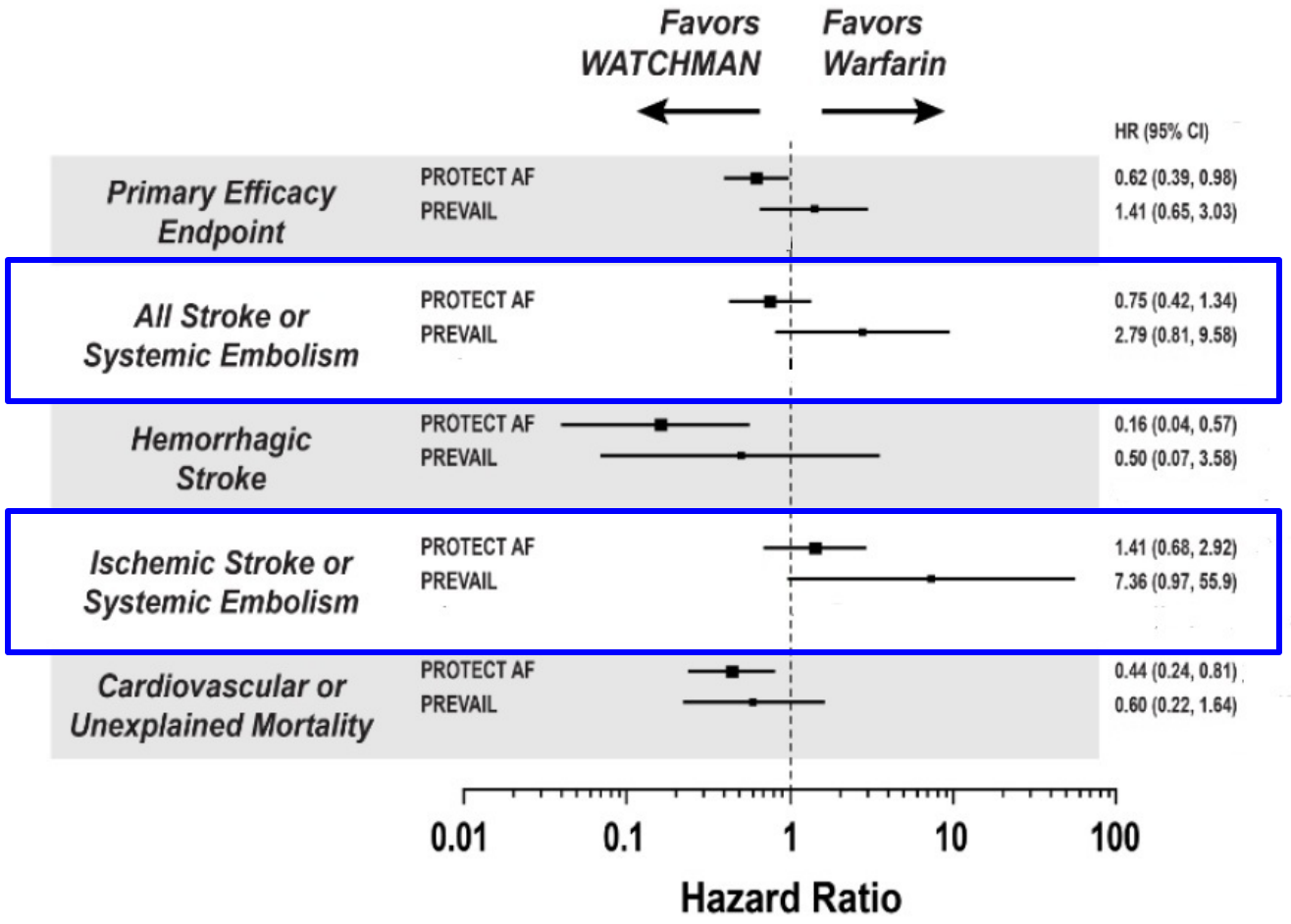

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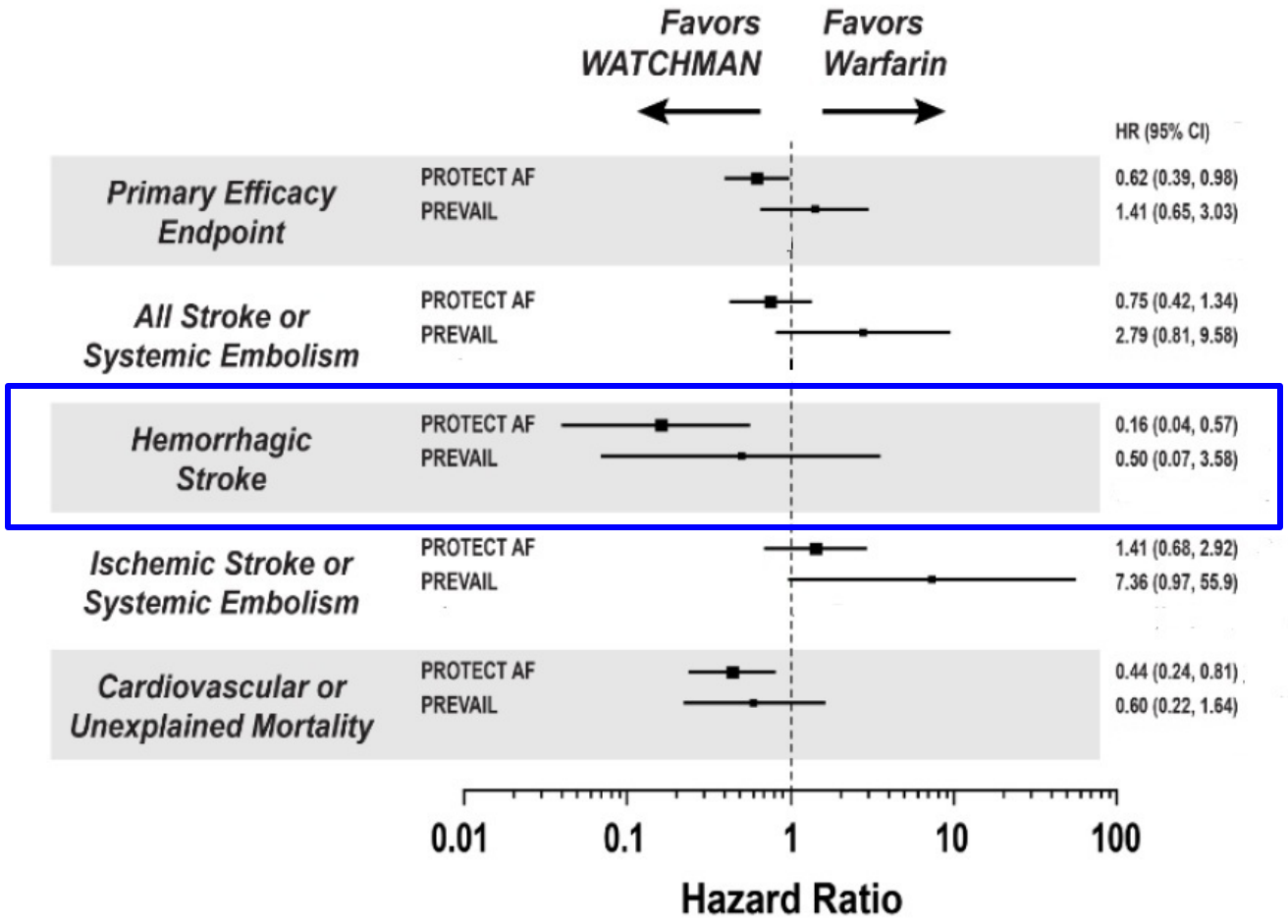

FDA Comments on the Sponsor's Patient Level Meta-Analysis

- Pools results from just 2 trials (PROTECT AF and PREVAIL) with divergent results
- Interpretation is limited by substantial differential follow-up and lack of covariate adjustment
- Recall that in the design of PREVAIL:
  - There was agreement between the sponsor and FDA that because of study conduct issues, the PROTECT AF data would be down-weighted 50%
  - The WATCHMAN device failed the non-inferiority test for both the first and second primary endpoints

Imputed Placebo Analysis: FDA Comments

- Supports the postulate that the WATCHMAN device is better than no treatment or ineffective treatment (ASA)
  - Acknowledges that warfarin superior to WATCHMAN for ischemic stroke
- Estimates ischemic stroke risk for untreated AF patients based on $CHADS_2$ and CHA_2DS_2-VASc scores
  - Conclusions drawn from statistical comparisons across different trials are limited by known and unknown differences in patient populations and trial conduct
- There are no randomized studies comparing WATCHMAN to no therapy or antiplatelet therapy

Indications for Use

The WATCHMAN LAAC Device is indicated to prevent thromboembolism from the left atrial appendage. The device may be considered for patients with non-valvular atrial fibrillation who, based on $CHADS_2$ or CHA_2DS_2-VASc scores, would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism.

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The WATCHMAN LAAC Device is indicated to prevent thromboembolism from the left atrial appendage. The device may be considered for patients with non-valvular atrial fibrillation who, based on $CHADS_2$ or CHA_2DS_2-VASc scores, would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism.

Interpretation of the Indications for Use Statement

- The WATCHMAN device may be considered in patients at risk for stroke and for whom warfarin would be recommended
  - Language specific to patients recommended for warfarin
    - Does not apply to patients for whom a NOAC would be recommended
      - The safety and effectiveness of the WATCHMAN device has not been compared to the NOACs
    - Does not apply to patients with absolute or relative contraindications to oral anticoagulation
      - The safety and effectiveness of the WATCHMAN device has not been compared to no therapy or antiplatelet therapy

Clinical Review Concluding Remarks

- Despite a proven highly favorable benefit-risk profile, oral anticoagulation is under-utilized in AF patients who are at increased risk for ischemic stroke (IS) and systemic embolism (SE), primarily due to concerns about bleeding complications.
- If thromboembolism from the LAA is the predominate mechanism for IS and SE, interventions that occlude the LAA orifice might offer an alternative to anticoagulation.
- The PROTECT AF trial showed the potential utility of the WATCHMAN device but was not adequate for FDA approval.

Clinical Review Concluding Remarks

- The PREVAIL trial was developed to address the limitations of the PROTECT AF study and at the same time, by utilizing a Bayesian design, efficiently collect additional safety and effectiveness data on the WATCHMAN device.
  - FDA and the Sponsor reached consensus on the design elements of PREVAIL, particularly the use of prior data from PROTECT AF, which would be down-weighted 50%
- PREVAIL demonstrated that WATCHMAN device implantation could be reasonably safe with an acceptable operator learning curve

Clinical Review Concluding Remarks

- In the PREVAIL Bayesian analysis of the updated June 2014 dataset, the WATCHMAN device:
  - *Failed to meet* the non-inferiority endpoint compared to warfarin for the composite of all stroke, systemic embolism, and CV or unexplained death
  - *Failed to meet* the non-inferiority endpoint compared to warfarin for ischemic stroke and systemic embolism events occurring after 7 days post-device implantation

Clinical Review Concluding Remarks

- In determining whether the WATCHMAN device is an acceptable alternative to warfarin and evaluating whether the totality of the data support a reasonable assurance of safety and effectiveness, the Panel is being asked to address the following questions that are critical to the benefit-risk assessment of the device:
  - Does the WATCHMAN device provide adequate protection from ischemic stroke and systemic embolism in at-risk patients with non-valvular atrial fibrillation?
  - Is the avoidance of long-term warfarin use following successful implantation of the WATCHMAN device associated with a reduced risk of hemorrhagic stroke?
  - Is there a clinically important signal of reduced major bleeding complications due the avoidance of long-term use of anticoagulation therapy in patients treated with the WATCHMAN device?

FDA Presentations

- Introduction and Regulatory History – Dr. Rachel Neubrander
- Clinical Presentation – Dr. Andrew Farb
- Statistical Presentation – Dr. Manuela Buzoianu
- Summary – Dr. Rachel Neubrander

WATCHMAN Left Atrial Appendage Closure Therapy - Statistical Evaluation -

Manuela Buzoianu, PhD
Division of Biostatistics
Office of Surveillance and Biometrics
Food and Drug Administration
October 8, 2014

Outline

- Bayesian statistics
- Updated PREVAIL study
  - Pre-specified Bayesian analysis
  - The PROTECT AF informative prior
  - The divergence between PROTECT AF prior and PREVAIL only
- Summary

Bayesian Statistics

Approach for learning from evidence as it accumulates

- Prior distribution on quantity of interest
- The likelihood of new data (via model)
- Posterior distribution on quantity of interest
  - Updated prior distribution by new data
  - Bayesian statistical inference (e.g. point and interval estimates)

Updating Bayesian Statistics

As evidence accumulates in iterative fashion

- Additional data is acquired
- Updated Posterior distribution
  - Updated distribution by additional new data
  - Updated Bayesian inference (e.g. point and interval estimates)

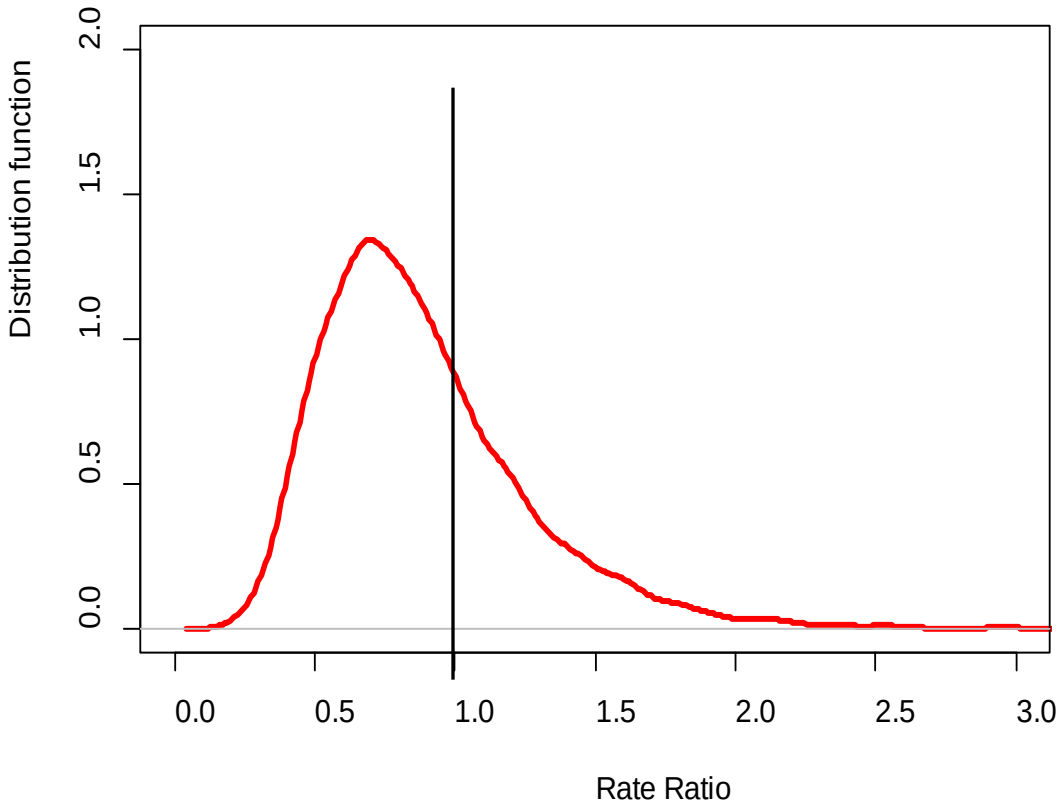
PREVAIL Study Primary Analysis – First and Second Primary Endpoints

- Pre-specified Bayesian modeling approach
  - Informative prior based on PROTECT AF data with 50% discount
  - Model event rate data via a piecewise exponential model with rate assumed constant on 4 time intervals
    - 0 - 7 days
    - 8 - 60 days
    - 61 - 182 days,
    - 183+ days

The informative prior

- The new trial, PREVAIL, borrows “strength” from the prior study, PROTECT AF
- The PROTECT AF prior data were down-weighted 50%, resulting in a total of 618.8 pt-yrs
- Assure that the prior information is not too “informative” (overwhelms PREVAIL data only)
- Probability of study claim based on the prior only should be less than 97.5% (success criterion for the posterior probability)

The informative prior for PREVAIL first primary endpoint (18-month rate ratio)

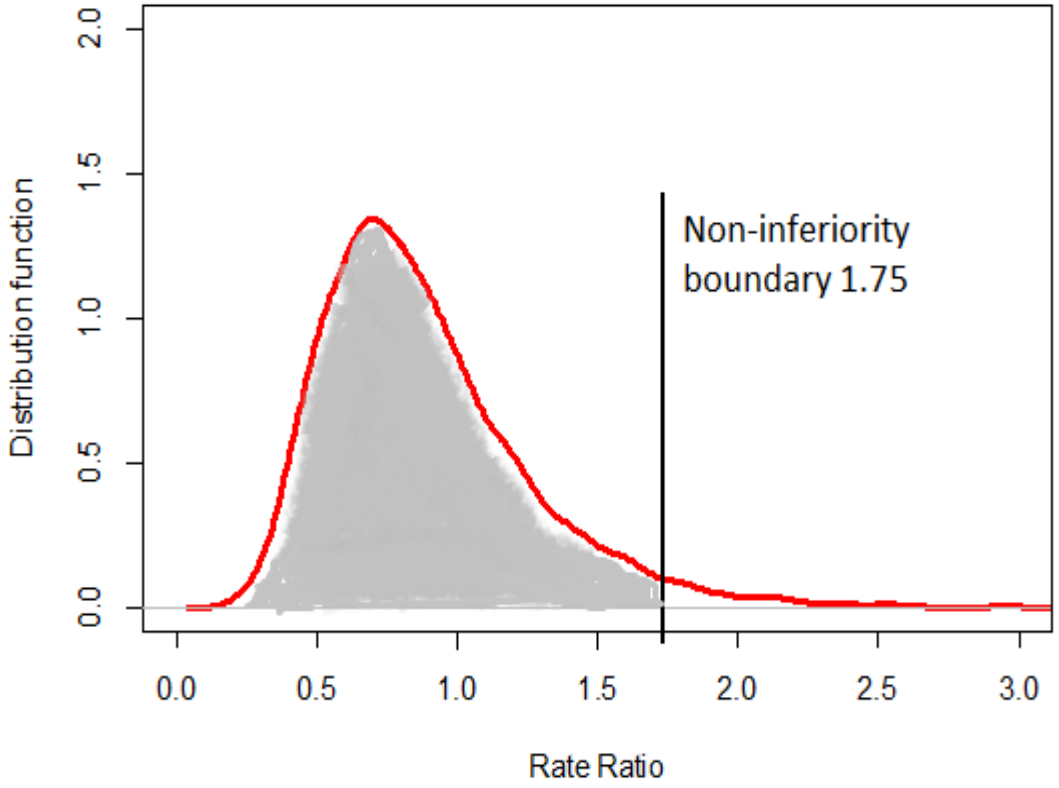


18-month rate

- device: 0.062
- control: 0.077

18-month rate ratio 0.88

The informative prior for PREVAIL first primary endpoint (18-month rate ratio)



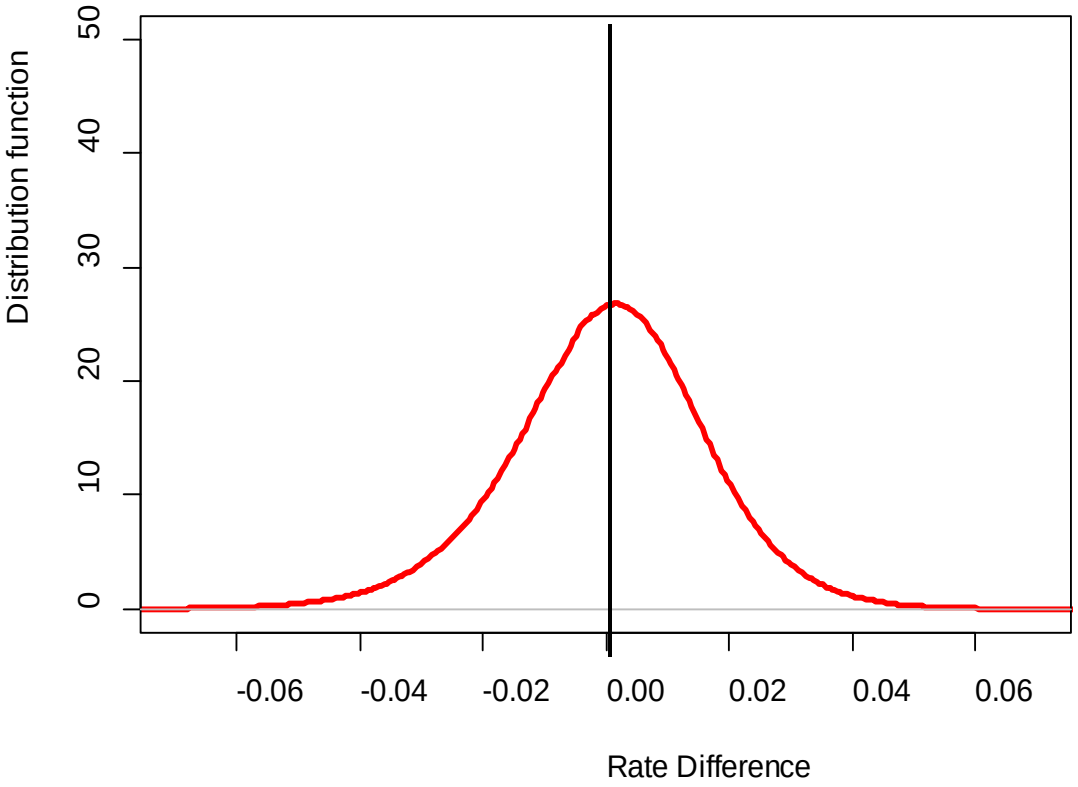
18-month rate
- device: 0.062
- control: 0.077

18-month rate ratio 0.88

Prior probability of non-inferiority (rate ratio < 1.75)
= 97.1%

(Success criterion for probability of non-inferiority: 97.5%)

The informative prior for PREVAIL second primary endpoint (18-month rate difference)

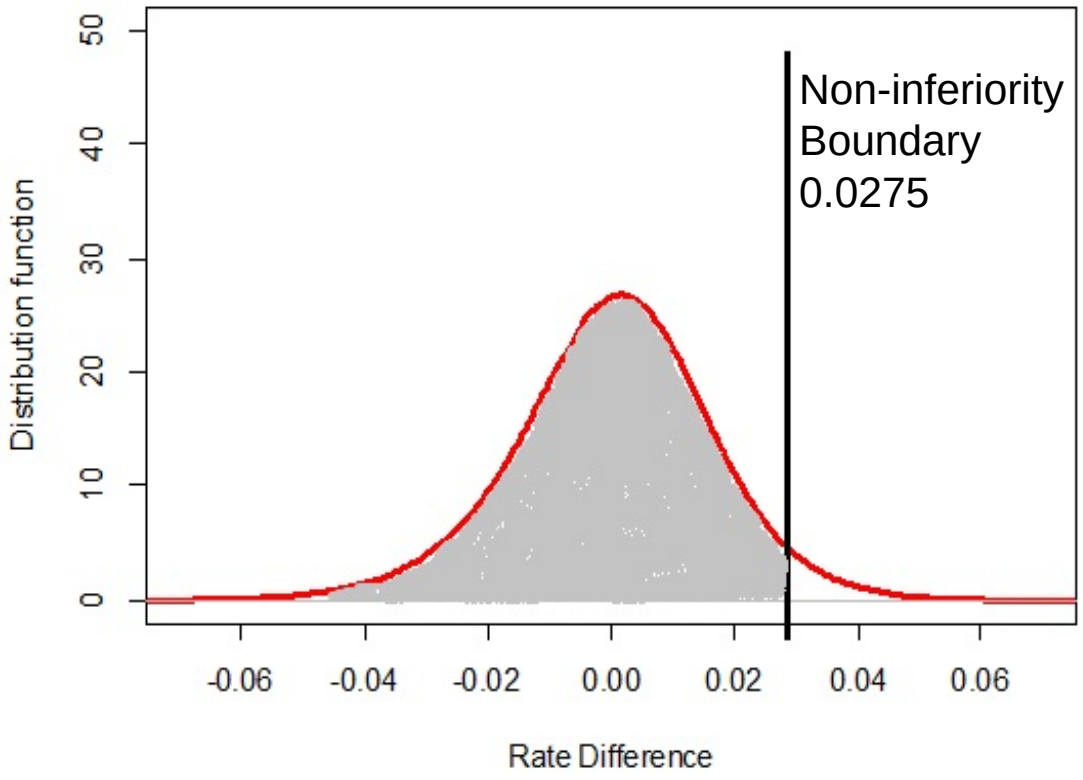


18-month rate

- device: 0.025
- control: 0.025

18-month rate difference 0.0003

The informative prior for PREVAIL second primary endpoint (18-month rate difference)



18-month rate

- device: 0.025
- control: 0.025

18-month rate difference 0.0003

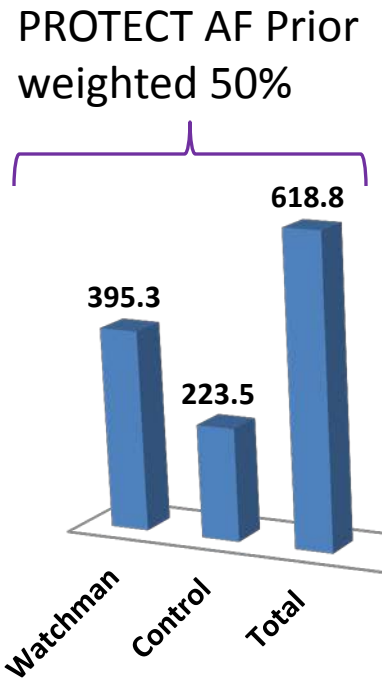
Prior probability of non-inferiority (rate difference < 0.0275) = 95.7%

(Success criterion for probability of non-inferiority: 97.5%)

Updated PREVAIL only

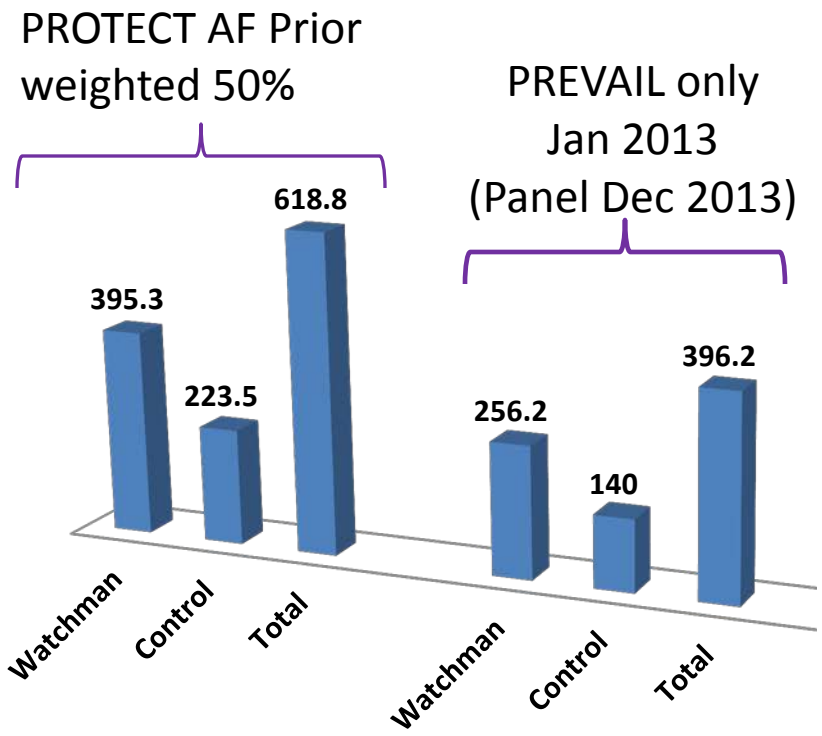
- 407 randomized subjects (269 Watchman, 138 Control)
- Dataset presented at Panel December 2013
  - Locked January 2013
  - 28% subjects reached 18-month follow-up
  - Mean follow-up 11.8 ± 5.8 months
- Data from June 2014
  - All subjects reached 18-month follow-up
  - Mean follow-up 25.9 ± 9.7 months

Size of prior information (PROTECT AF) vs. observed data (PREVAIL only)



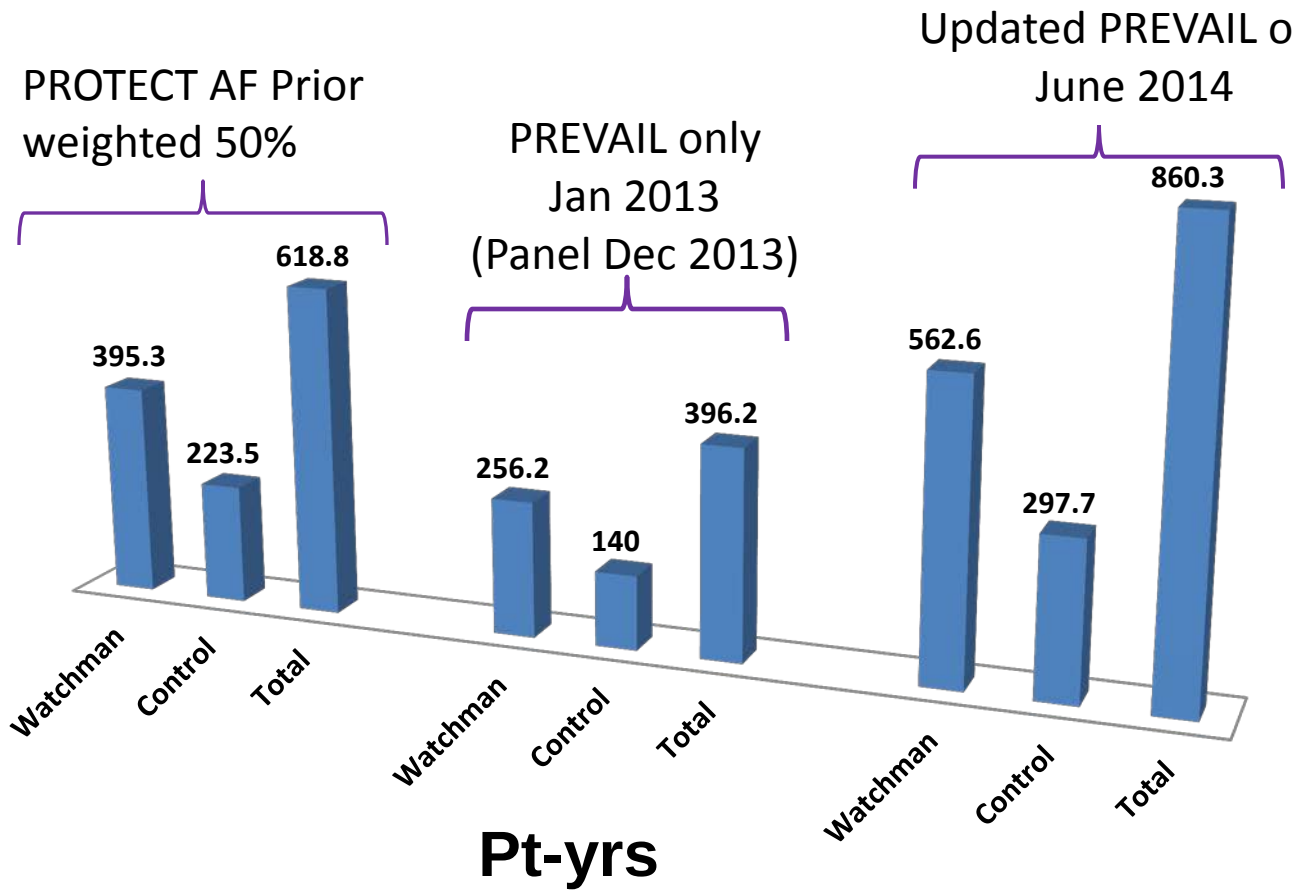
Pt-yrs

Size of prior information (PROTECT AF) vs. observed data (PREVAIL only)

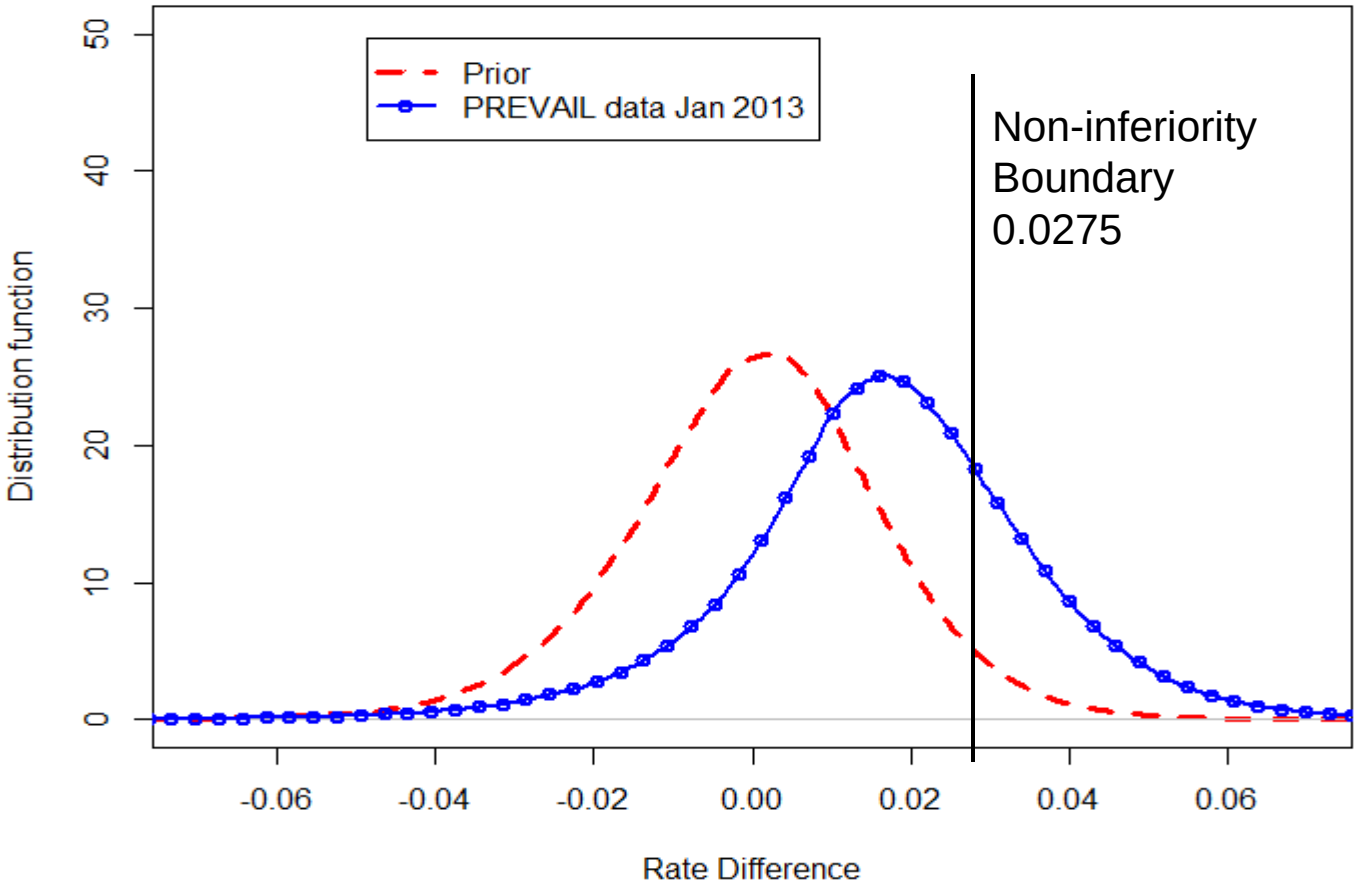


Pt-yrs

Size of prior information (PROTECT AF) vs. observed data (PREVAIL only)



The second primary endpoint – 18-month Rate Difference Distribution (PROTECT AF prior vs. PREVAIL only)

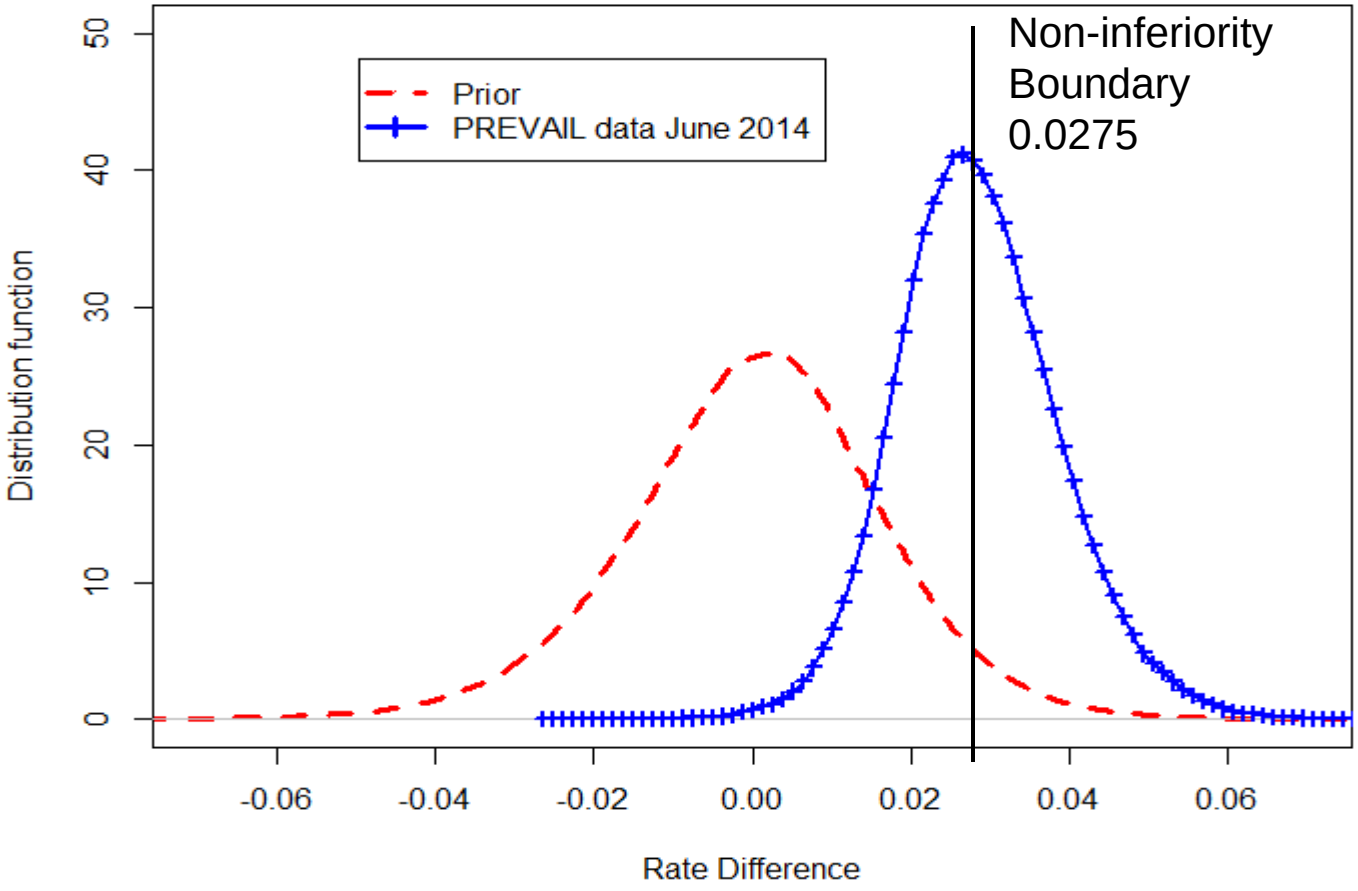


Prior/Posterior probability of non-inferiority:

Prior only = 95.7%

PREVAIL only Jan. 2013 = 73.6%

The second primary endpoint – 18-month Rate Difference Distribution (PROTECT AF prior vs. PREVAIL only)



Prior/Posterior probability of non-inferiority:

Prior only = 95.7%

PREVAIL only June 2014 = 48.8%

Updated PREVAIL Bayesian Analysis Primary Endpoints Results

First Primary Endpoint

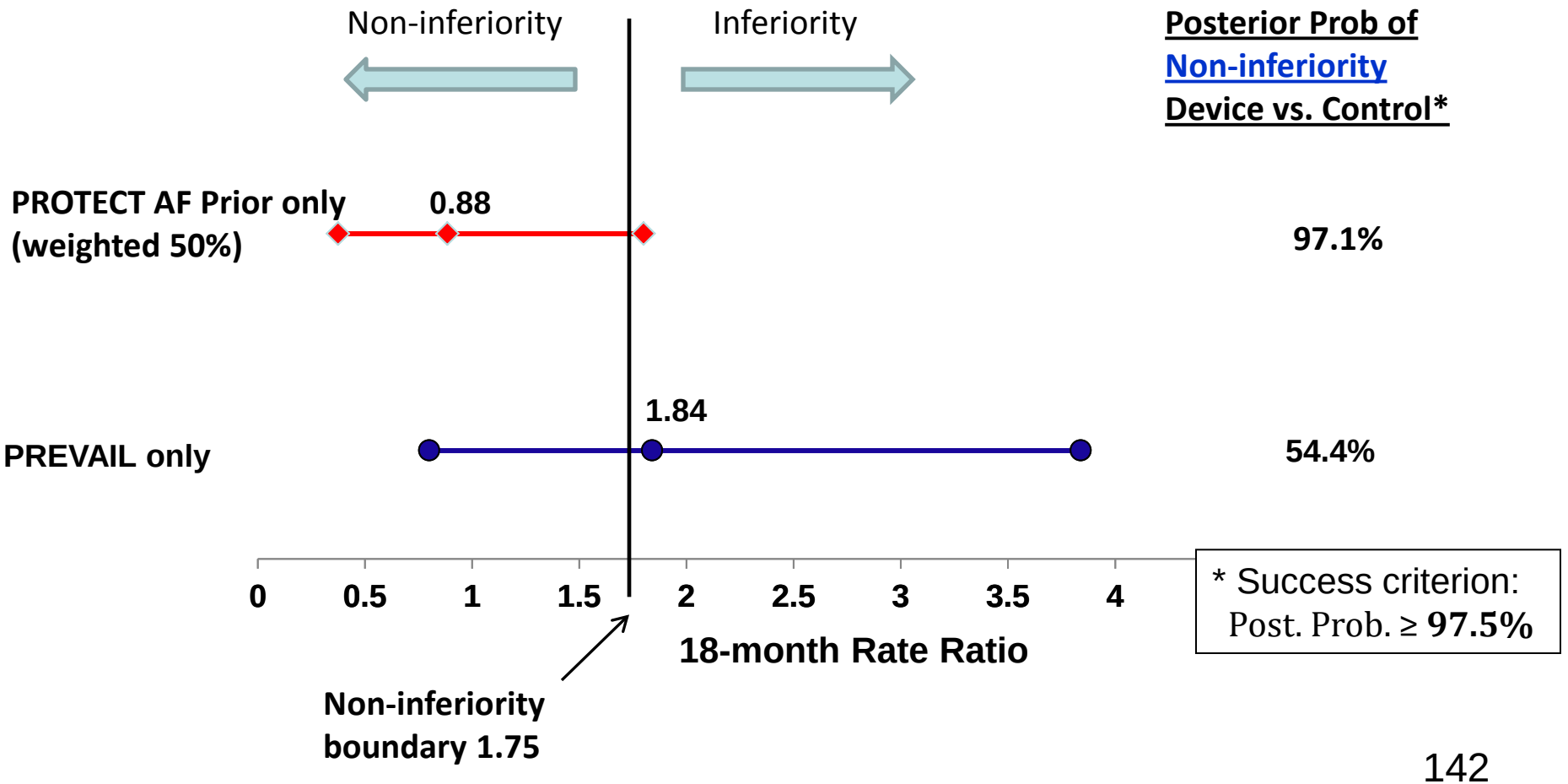
- Occurrence (18-month rates) of
  - stroke (ischemic/hemorrhagic)
  - death (cardiovascular/unexplained)
  - systemic embolism

Non-inferiority Criterion
Upper bound equitailed 2-sided 95% Credible Interval
for 18-month rate ratio < **1.75**

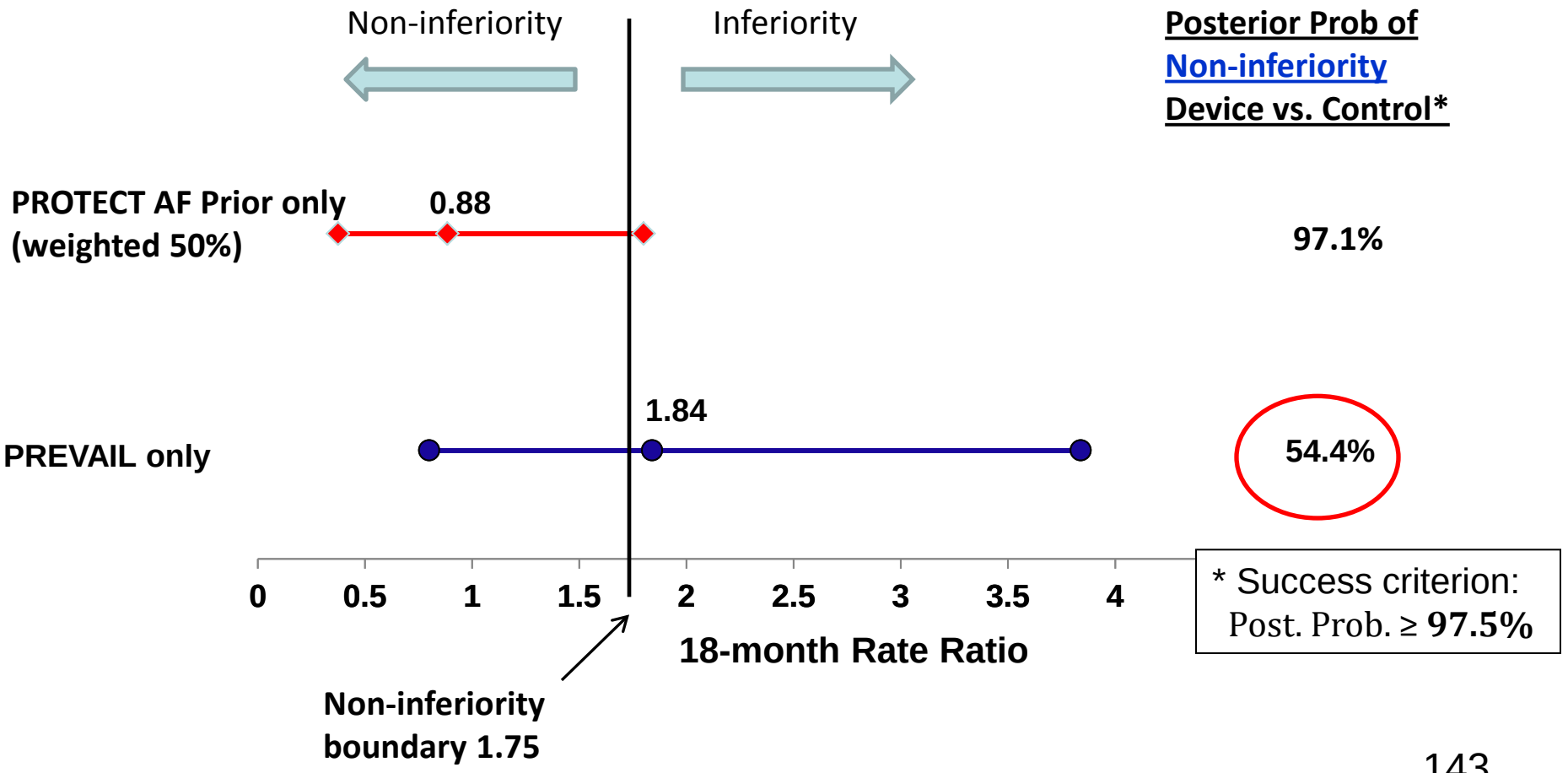
(Posterior probability of non-inferiority (rate ratio < 1.75) ≥ **97.5%**)

NOT MET
(upper bound 2.05)
(Posterior Probability = 92.6%)

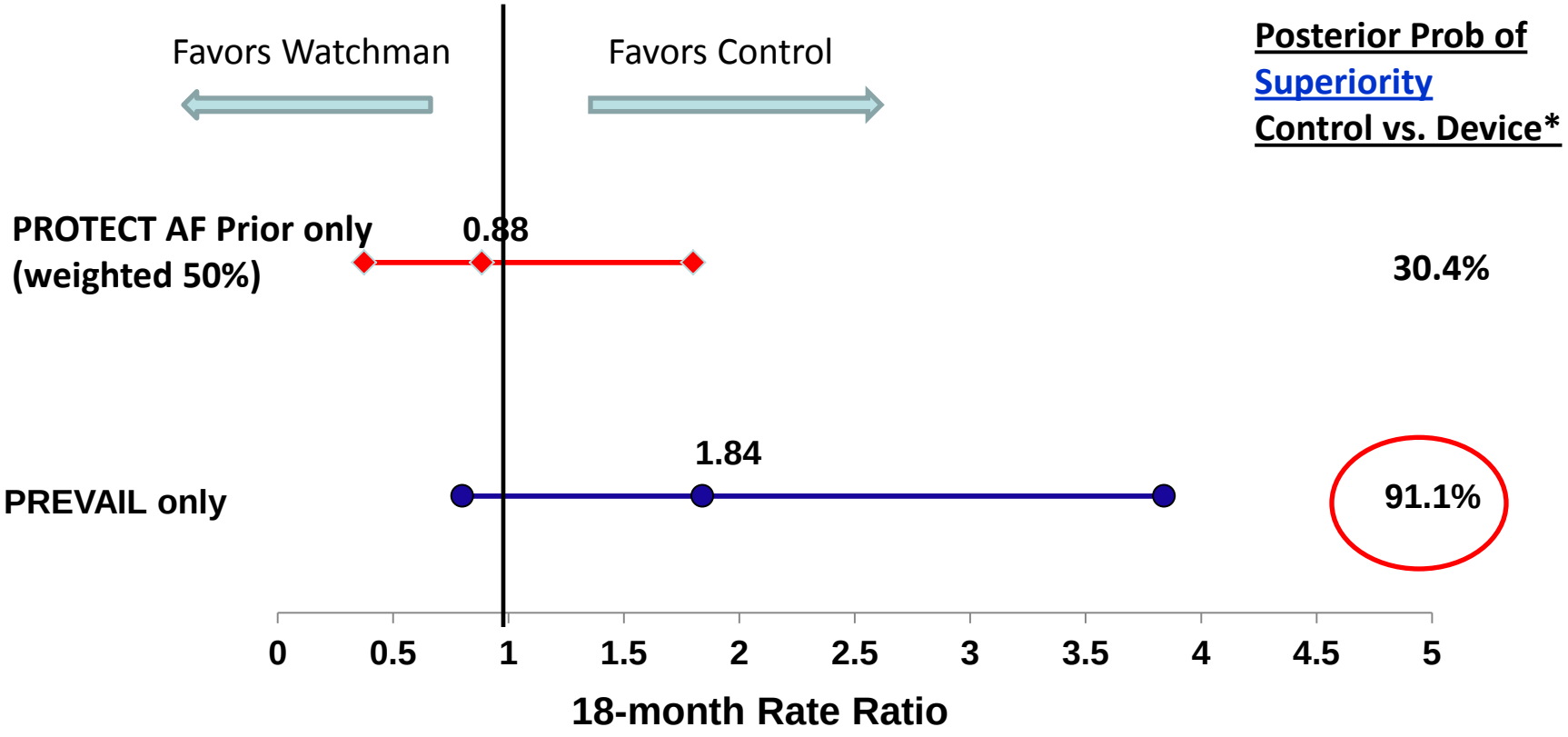
First Primary Endpoint Bayesian Analysis PROTECT AF prior vs. PREVAIL only



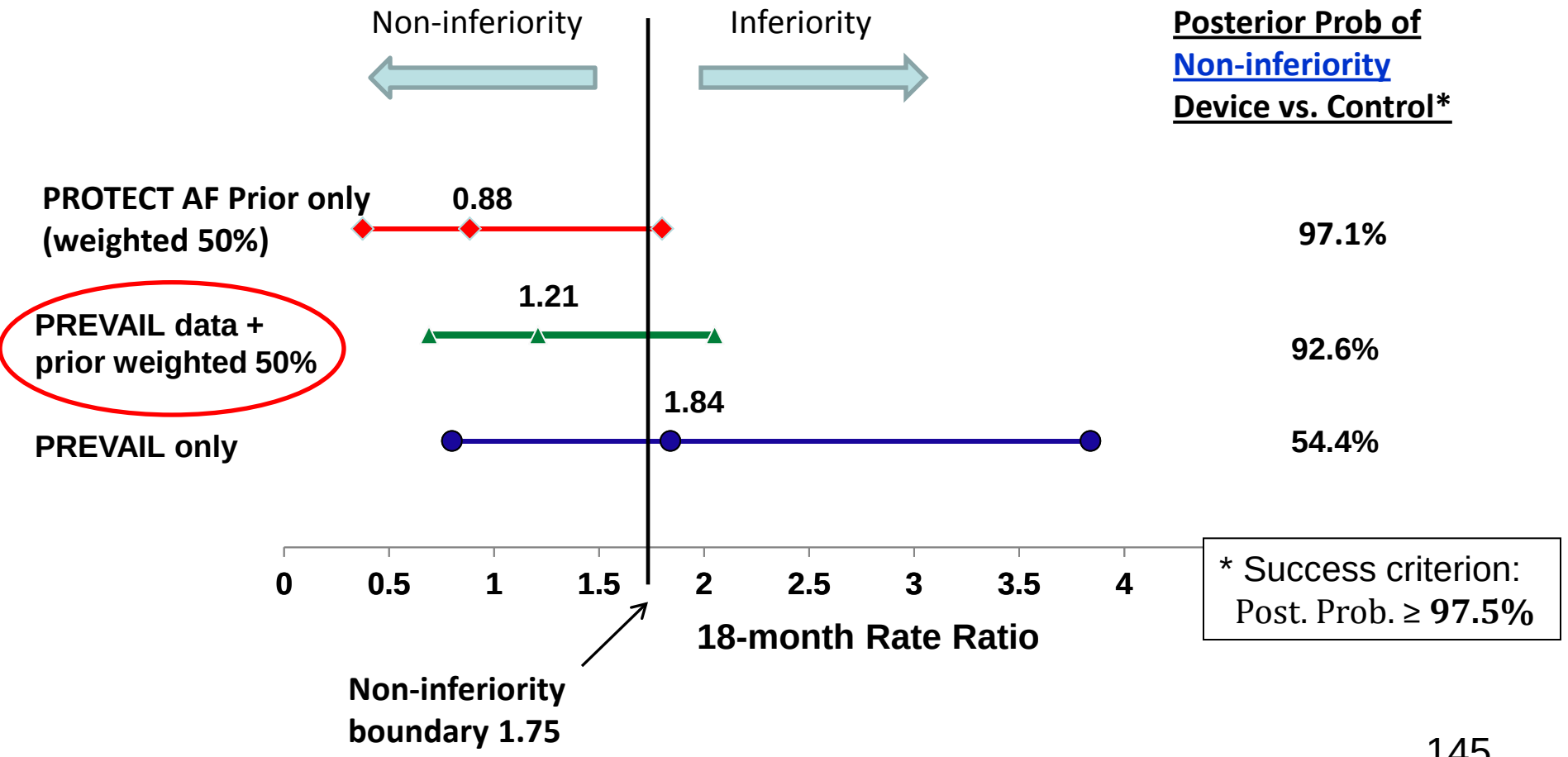
First Primary Endpoint Bayesian Analysis PROTECT AF prior vs. PREVAIL only



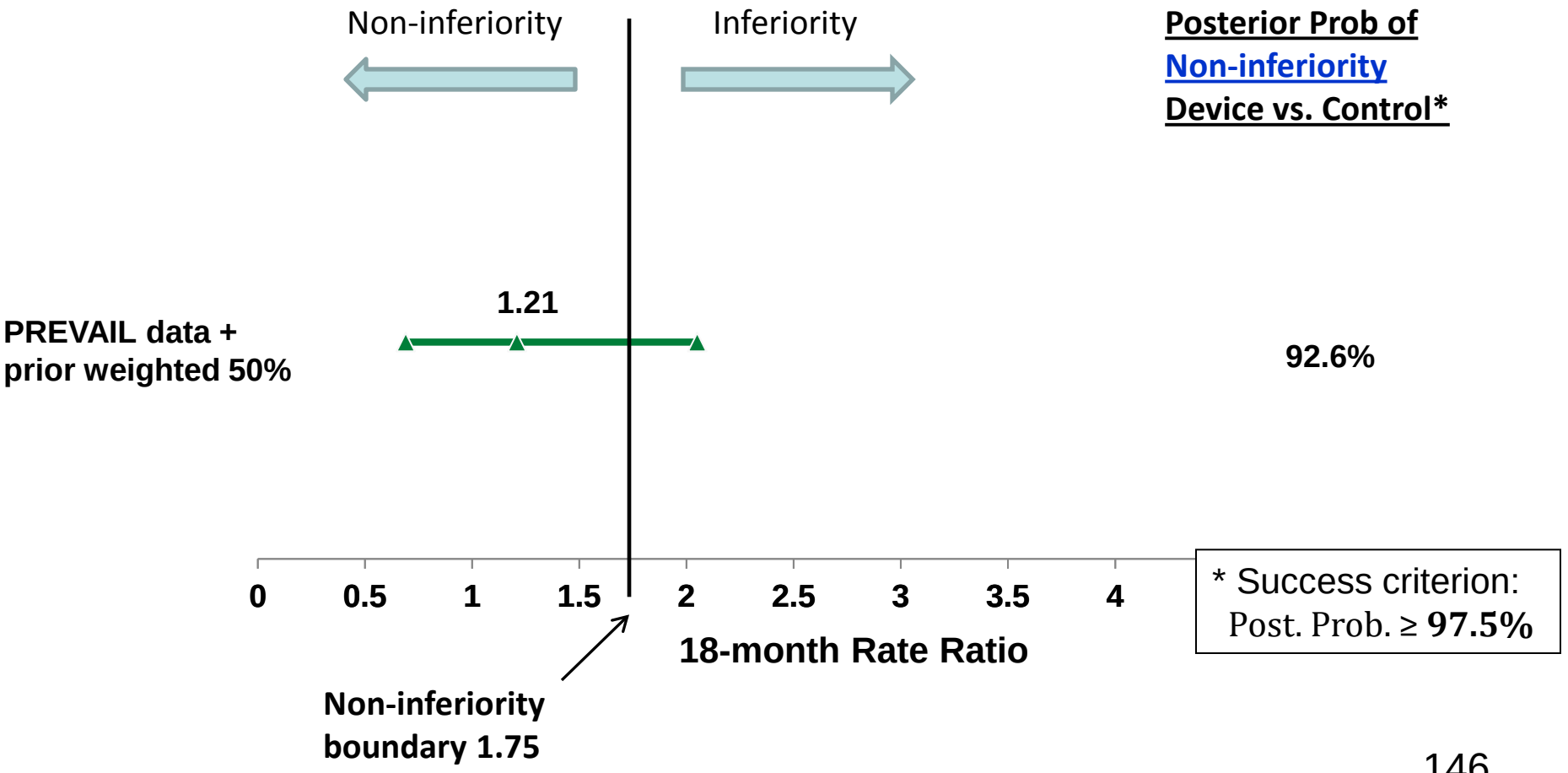
First Primary Endpoint Bayesian Analysis PROTECT AF prior vs. PREVAIL only



First Primary Endpoint
Pre-specified Bayesian Analysis



First Primary Endpoint
Pre-specified Bayesian Analysis



Second Primary Endpoint

- Occurrence (18-month [minus the first 7 days] rates) of ischemic stroke/systemic embolism

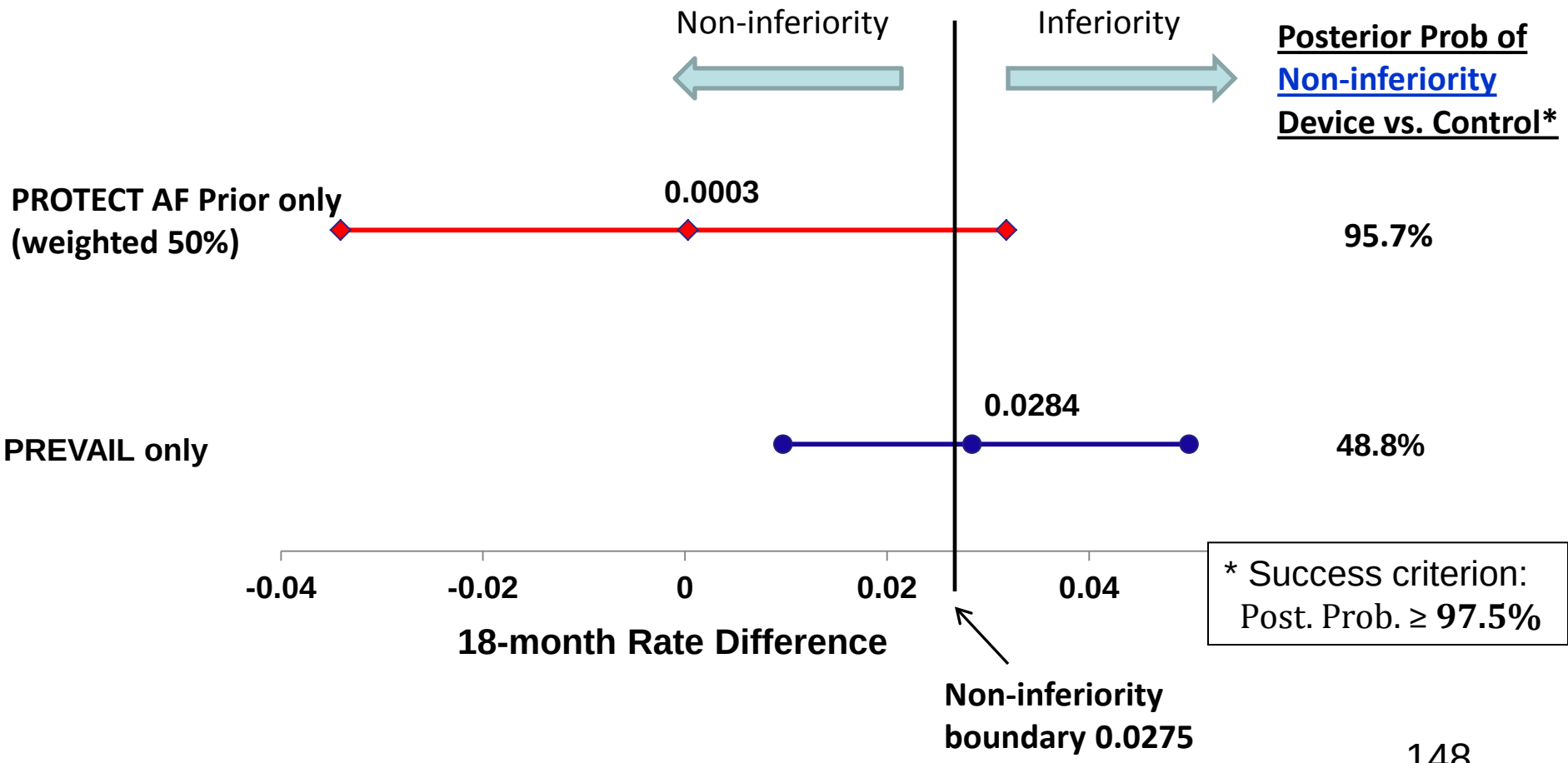
Non-inferiority Criterion

Upper bound equitailed 2-sided 95% Credible Interval for 18-month rate difference < 0.0275

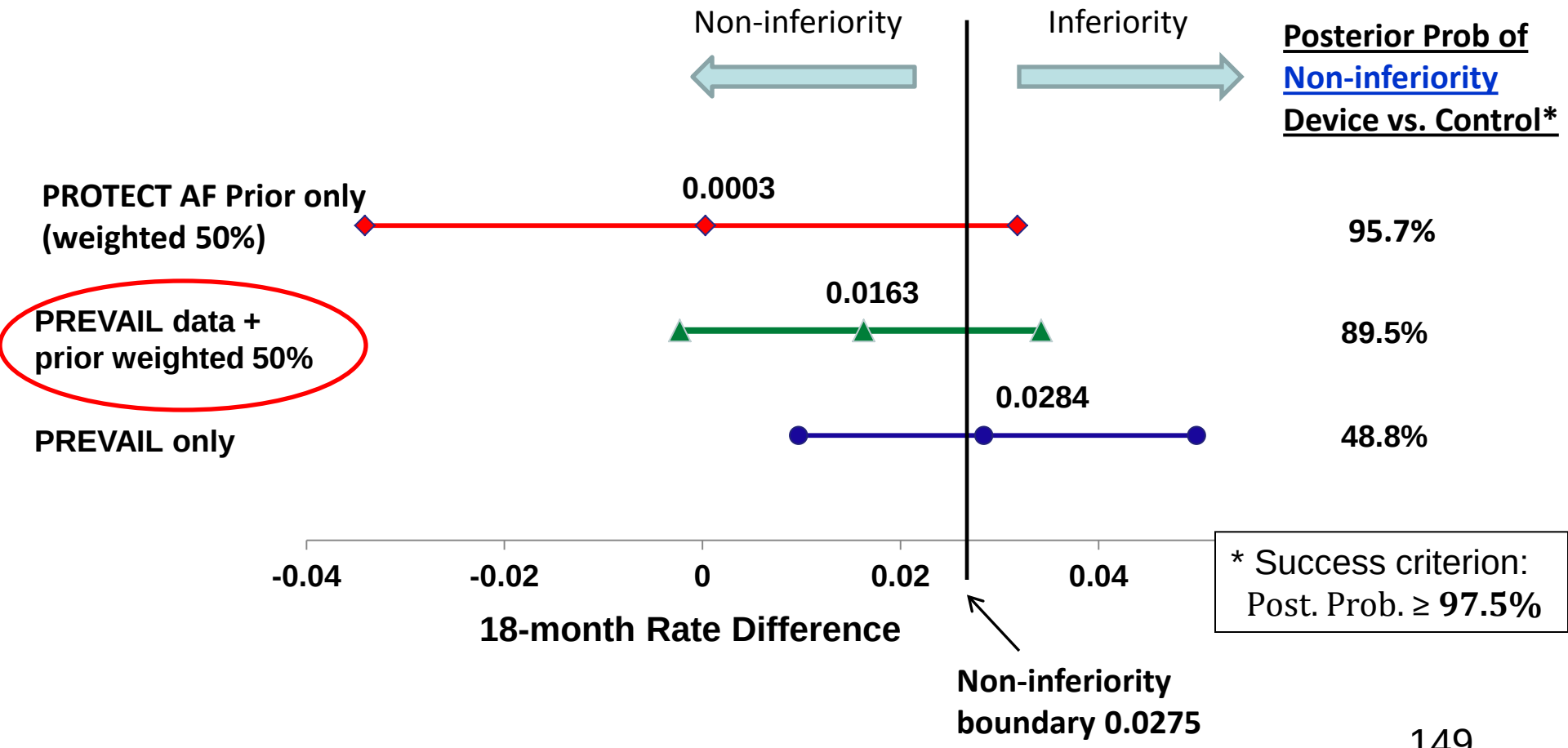
(Posterior probability of non-inferiority ≥ 97.5%)

NOT MET
(upper bound 0.0342)
(Posterior Probability = 89.5%)

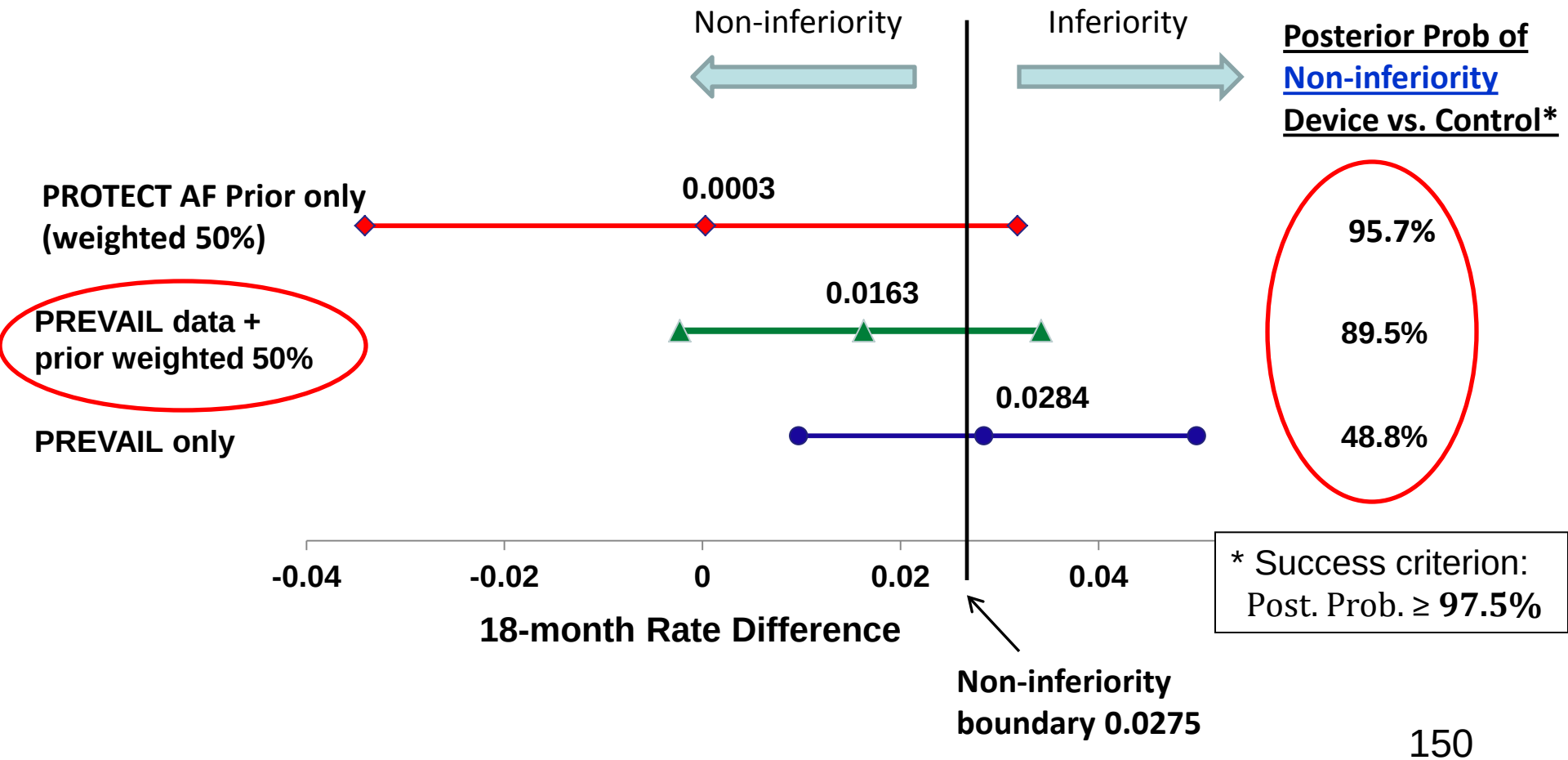
Second Primary Endpoint Bayesian Analysis PROTECT AF prior vs. PREVAIL only



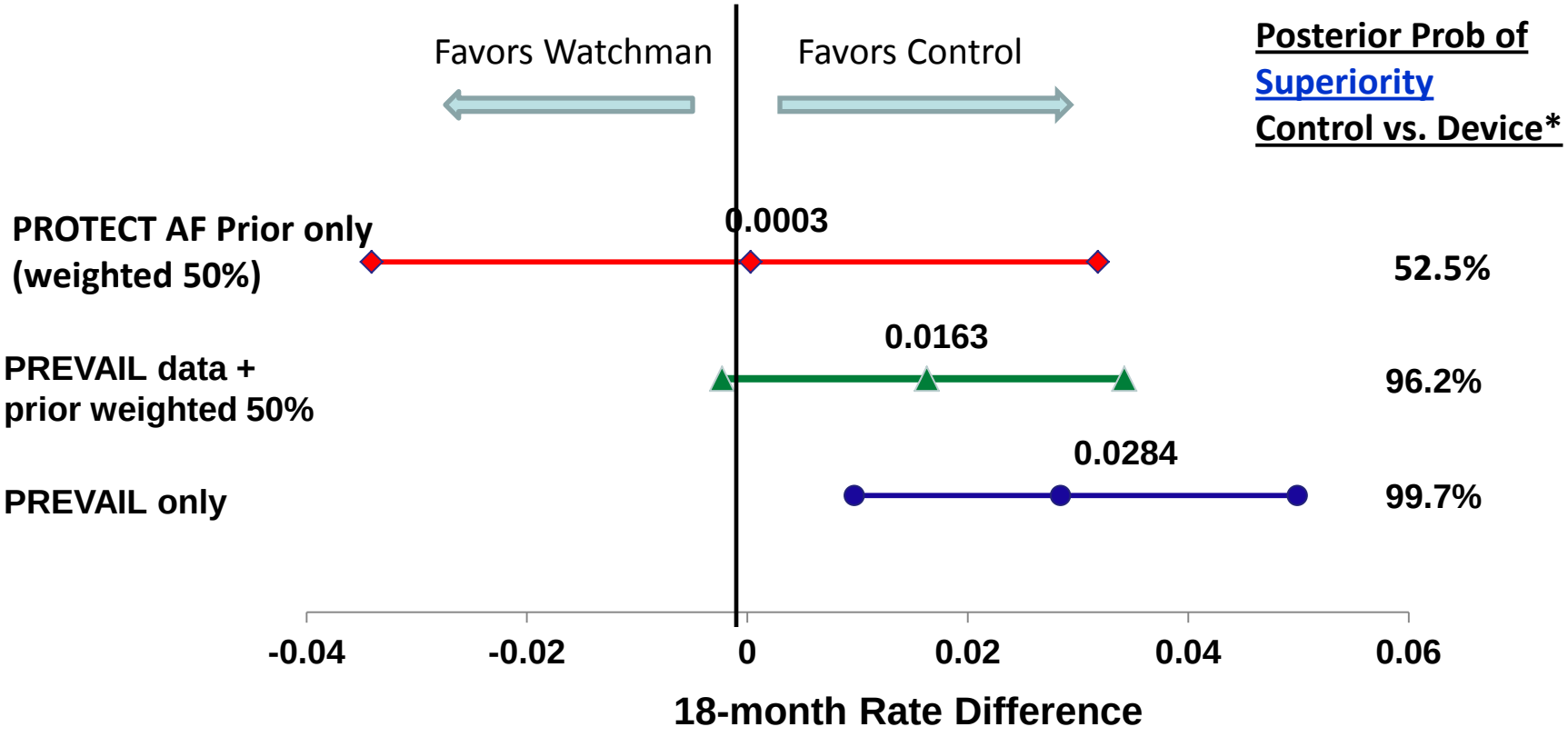
Second Primary Endpoint
Pre-specified Bayesian Analysis



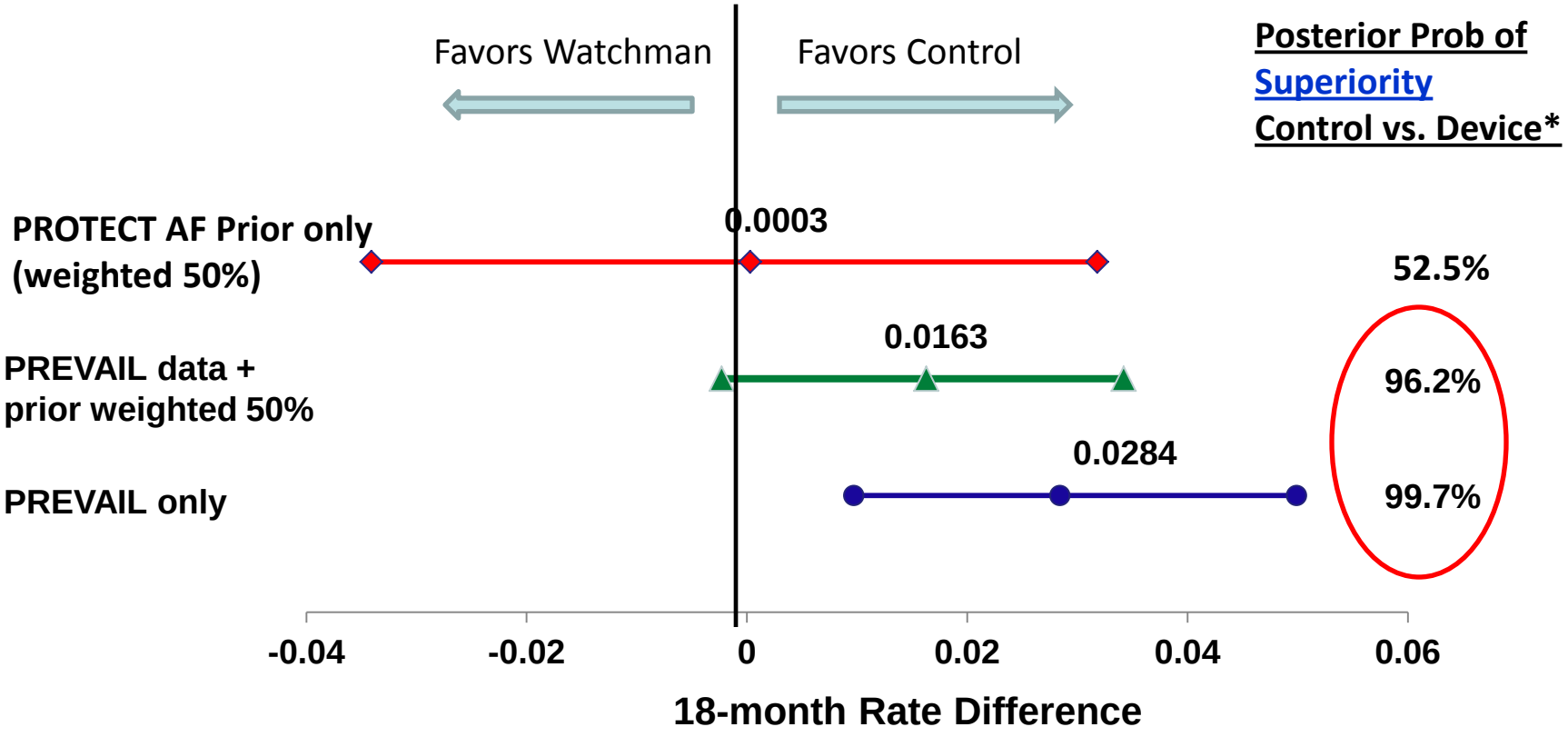
Second Primary Endpoint Bayesian Analysis



Second Primary Endpoint Bayesian Analysis



Second Primary Endpoint Bayesian Analysis



The PREVAIL study – Summary of Bayesian Analysis

- Pre-specified Non-inferiority Analysis
  - Substantial favorable prior information borrowed from PROTECT AF
  - In PREVAIL all subjects reached 18-month follow-up
  - First primary endpoint was not met
  - Second primary endpoint was not met
- The updated data shows significant divergence between PREVAIL results compared to the PROTECT AF prior

FDA Presentations

- Introduction and Regulatory History – Dr. Rachel Neubrander
- Clinical Presentation – Dr. Andrew Farb
- Statistical Presentation – Dr. Manuela Buzoianu
- Summary – Dr. Rachel Neubrander

FDA Summary

- New PREVAIL ischemic strokes raised concerns regarding the effectiveness of the WATCHMAN device.
- PREVAIL and PROTECT AF results diverge
  - Discordant outcomes from PROTECT AF and PREVAIL make evaluation of the totality of the data more challenging.
- WATCHMAN device failed to meet the first and second primary endpoints in the PREVAIL trial.

FDA Summary: Benefit-Risk

- Ischemic stroke and systemic embolism
  - PROTECT AF, PREVAIL-only and PREVAIL Bayesian analysis favor control group
  - PREVAIL-only control group event rate was lower than other anticoagulation trials

FDA Summary: Benefit-Risk

- Hemorrhagic stroke
  - Signal of reduced hemorrhagic stroke risk with WATCHMAN in PROTECT AF
  - PROTECT AF control group event rate was high compared to other anticoagulation trials
  - Clinical review of the individual hemorrhagic stroke events reduces robustness of this signal

FDA Summary: Benefit-Risk

- Cardiovascular/unexplained death
  - In PROTECT AF, mortality difference favoring the WATCHMAN device is driven by reduction in fatal hemorrhagic strokes, but clinical circumstances should be considered when attributing this benefit to the device
  - Non-hemorrhagic stroke events favored WATCHMAN, but were unlikely related to the device or warfarin

FDA Summary: Benefit-Risk

- Bleeding
  - Signal of reduced late bleeding in WATCHMAN subjects
  - No difference in overall bleeding rates

WATCHMAN Left Atrial Appendage Closure (LAAC) Technology

FDA Review of P130013

October 8, 2014

WATCHMAN Left Atrial Appendage Closure (LAAC) Technology

P130013

Panel Questions

Question 1

The WATCHMAN device is a locally targeted intervention that is intended to reduce the risk of ischemic stroke and systemic embolism by preventing the embolization of thrombi formed in the left atrial appendage. The rates of ischemic stroke and systemic embolism favored the Control group in both the PROTECT AF and PREVAIL-only updated datasets.

In addition, for the second primary endpoint in PREVAIL, non-inferiority was not met based on the updated June 2014 dataset.

Question 1

Please comment on the clinical significance of the results from PROTECT AF and PREVAIL, and discuss whether the WATCHMAN device is sufficiently comparable to warfarin in reducing the risk of ischemic stroke in patients with non-valvular AF.

Question 2

The results of the PROTECT AF trial suggest that the WATCHMAN device offers an important benefit compared with warfarin therapy by lowering the risk of hemorrhagic stroke. This signal of reduced risk of hemorrhagic stroke in WATCHMAN subjects was not observed in PREVAIL. However, the robustness of this signal is limited by the observation that the hemorrhagic stroke rate in the PROTECT AF control group was higher than expected and higher than warfarin groups in contemporary anticoagulation trials, and by circumstances regarding PROTECT AF control subjects who were adjudicated as having hemorrhagic stroke.

Question 2

Please comment on the potential benefit and the magnitude of the benefit of the WATCHMAN device to reduce the risk of hemorrhagic stroke compared to warfarin.

Question 3

Based on the June 2014 PREVAIL dataset, in the updated Bayesian analysis that combines the PREVAIL data with 50% discounted data from PROTECT AF, the WATCHMAN device continues to not meet the non-inferiority criteria for the first primary endpoint, and no longer meets the non-inferiority criteria for the second primary endpoint. In addition, an increasing divergence between the results of PROTECT AF and PREVAIL is present.

Please comment on the clinical significance of the failure of the WATCHMAN device to meet either of the first and second primary endpoints in the PREVAIL trial.

Question 4

A potential benefit of the WATCHMAN device compared to warfarin is a reduction in long-term bleeding complications associated with the use of chronic anticoagulation therapy. Bleeding events in the WATCHMAN group in PREVAIL-only and PROTECT AF were clustered in the peri-procedural period. Late bleeding rates favored the WATCHMAN group in both PROTECT AF and PREVAIL-only. However, there was no overall advantage of the WATCHMAN device vs. warfarin with respect to bleeding.

Please comment on the clinical significance of the major bleeding events.

Question 5

The sponsor has proposed the following Indications for Use:

"The WATCHMAN LAAC Device is indicated to prevent thromboembolism from the left atrial appendage. The device may be considered for patients with non-valvular atrial fibrillation who, based on $CHADS_2$ or CHA_2DS_2-VASc scores, would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism."

Please comment on the Indications for Use statement.

Question 6

The sponsor has presented comprehensive data from two randomized controlled trials (PROTECT AF and PREVAIL) and two continued access registries (CAP and CAP2).

Based on the totality of the data, do the probable benefits of the WATCHMAN device outweigh the probable risks?

In answering this question, please comment on the topics on the next slide.

Question 6

a. Do the results of PREVAIL and PROTECT AF support the central role of thromboembolism from the LAA in the pathogenesis of ischemic stroke in patients with non-valvular atrial fibrillation? Please comment on the relative effectiveness of a local (WATCHMAN) vs. systemic (warfarin) therapy.

b. Do the safety and effectiveness results from PROTECT AF and PREVAIL indicate that the WATCHMAN device is a clinically acceptable alternative to warfarin therapy?

Question 7

Please discuss whether the proposed labeling is acceptable or whether modifications are recommended.

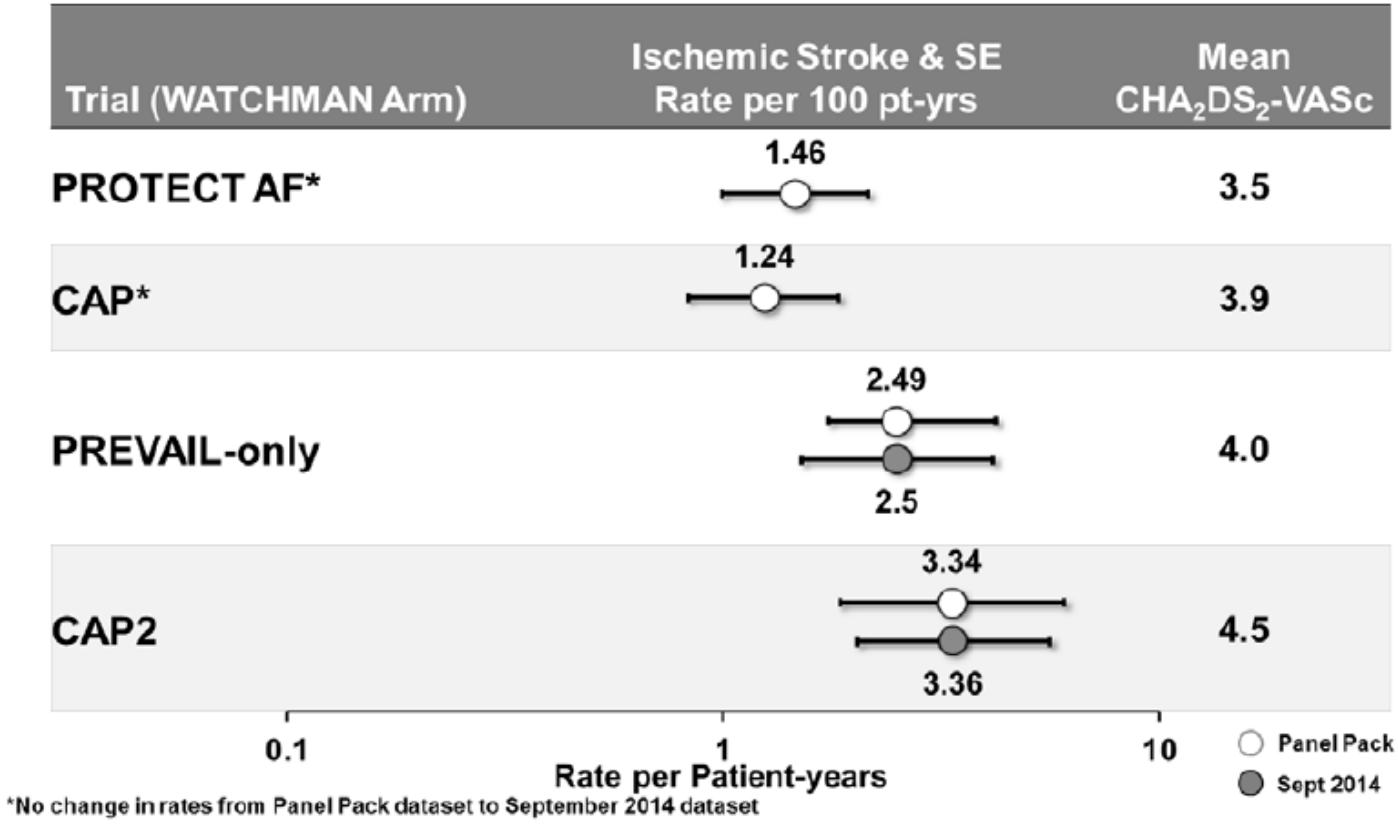
Question 8

In response to the recommendations from the December 2013 Panel, the sponsor increased the sample size of the proposed PAS to enroll 1000 new WATCHMAN subjects, which will be combined with 579 subjects currently enrolled in CAP2. For this combined WATCHMAN subject cohort, the PREVAIL primary endpoints will be tested against performance goals.

Given the new information from the WATCHMAN studies, please comment on the adequacy of the post-approval study and provide additional recommendations if needed.

Clinical Back-ups

Updated Ischemic Stroke or Systemic Embolism rates



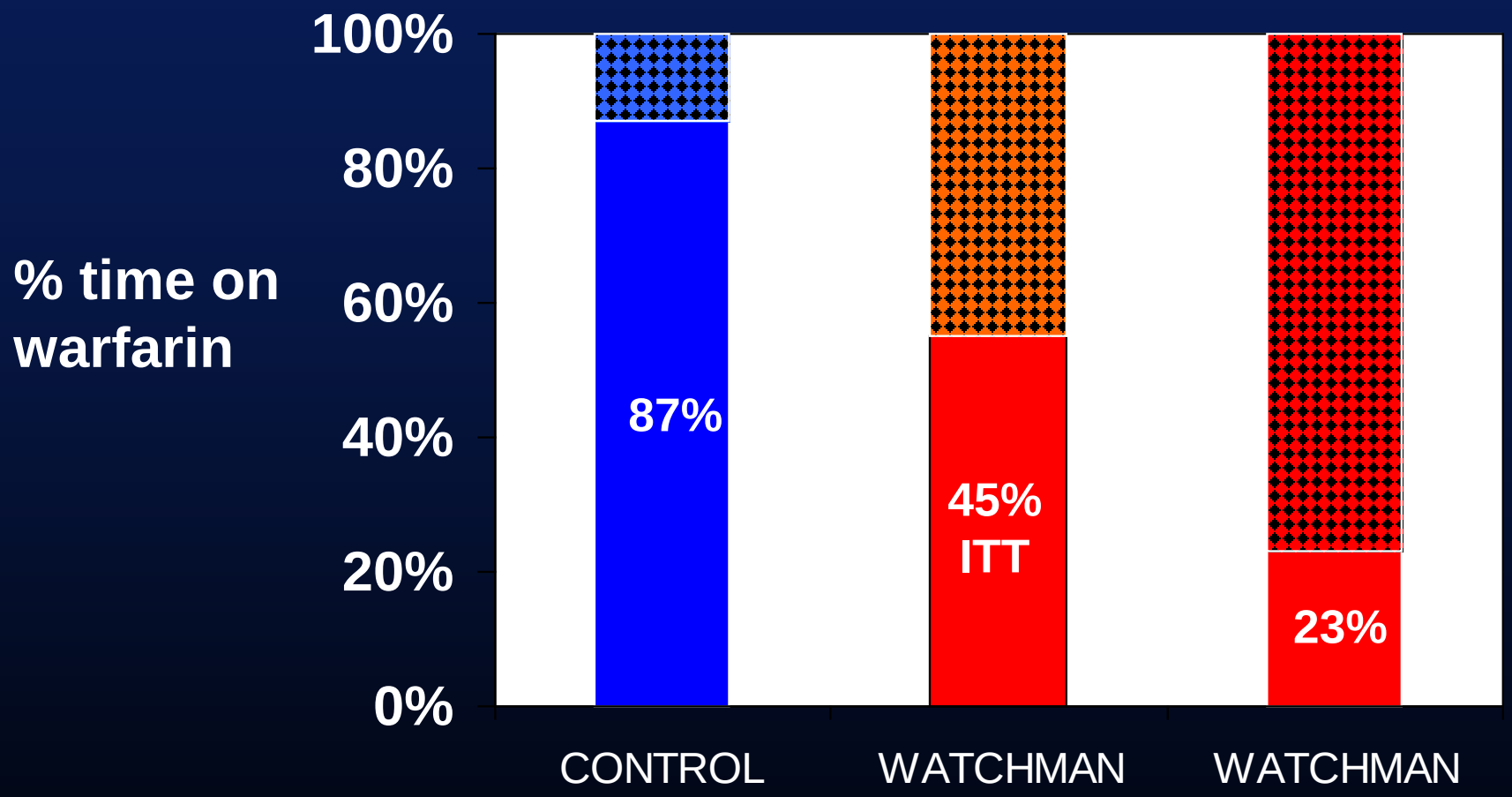
*No change in rates from Panel Pack dataset to September 2014 dataset

Updated Ischemic Stroke or Systemic Embolism rates

Trial (WATCHMAN Arm)	Ischemic Stroke & SE Rate per 100 pt-yrs	Mean CHA_2DS_2-VASc
PROTECT AF*	1.46	3.5
CAP*	1.24	3.9
PREVAIL-only	2.49 / 2.5	4.0
CAP2	3.34 / 3.36	4.5

*No change in rates from Panel Pack dataset to September 2014 dataset

Percent of Time on Warfarin
(% follow-up time on warfarin on per patient basis)

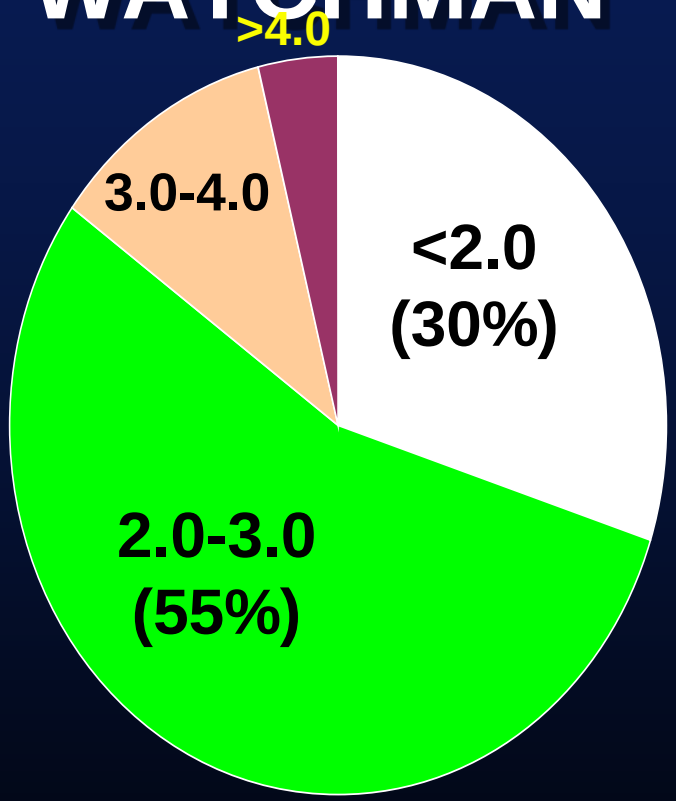


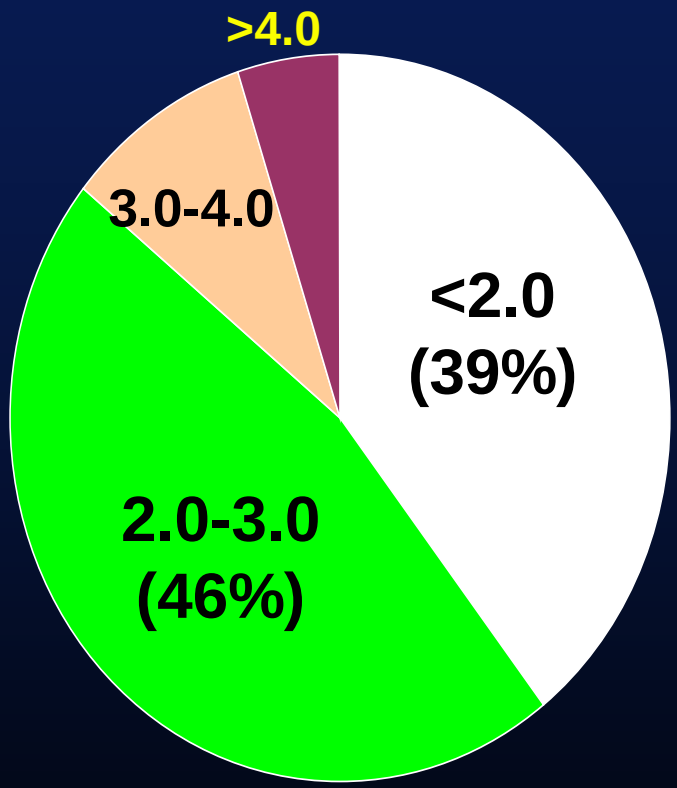
Summary of INR Measurements

(Note: not time in therapeutic range)

CONTROL

WATCHMAN



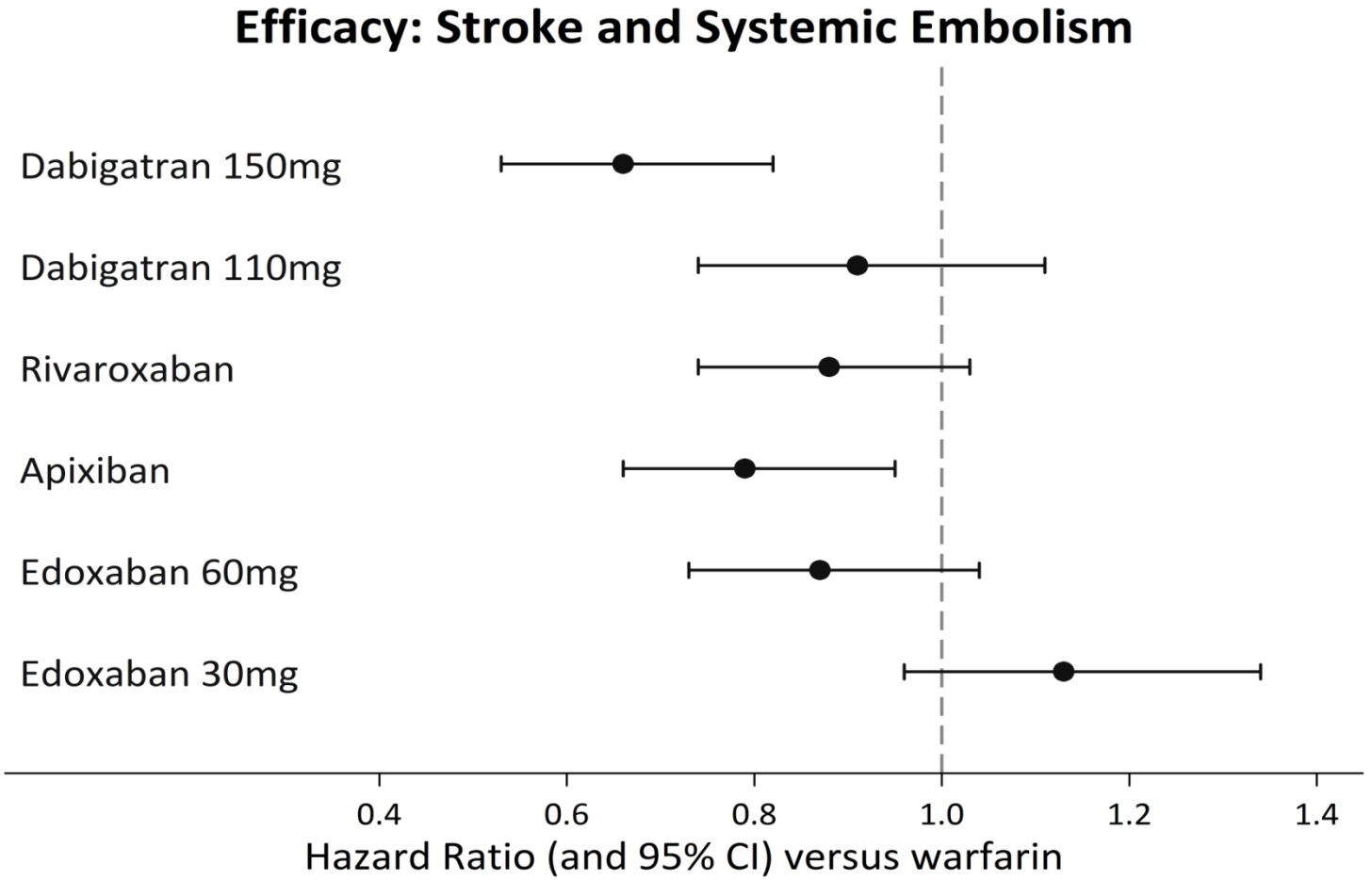


WATCHMAN Indications for Use (EU)

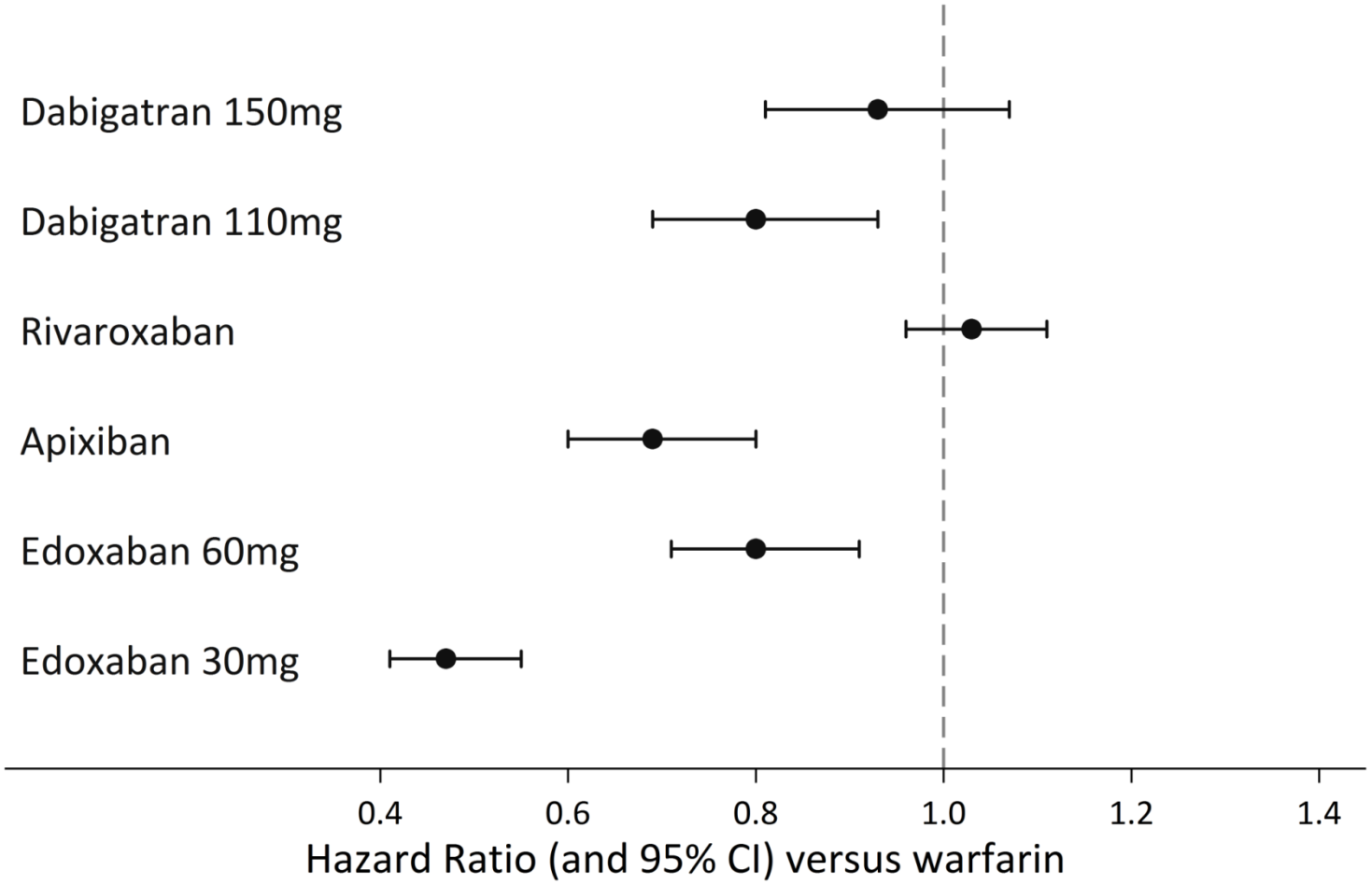
The WATCHMAN LAAC Device is intended to prevent thrombus embolization from the left atrial appendage and reduce the risk of life-threatening bleeding events in patients with non-valvular atrial fibrillation who are eligible for anticoagulation therapy or who have a contraindication to anticoagulation therapy.

Reference: http://www.bostonscientific.com/watchman-intl/watchman.html?

Comparisons of 4 new anticoagulants versus warfarin in the RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE trials



Safety: Major bleed



higher dose dabigatran has best efficacy?

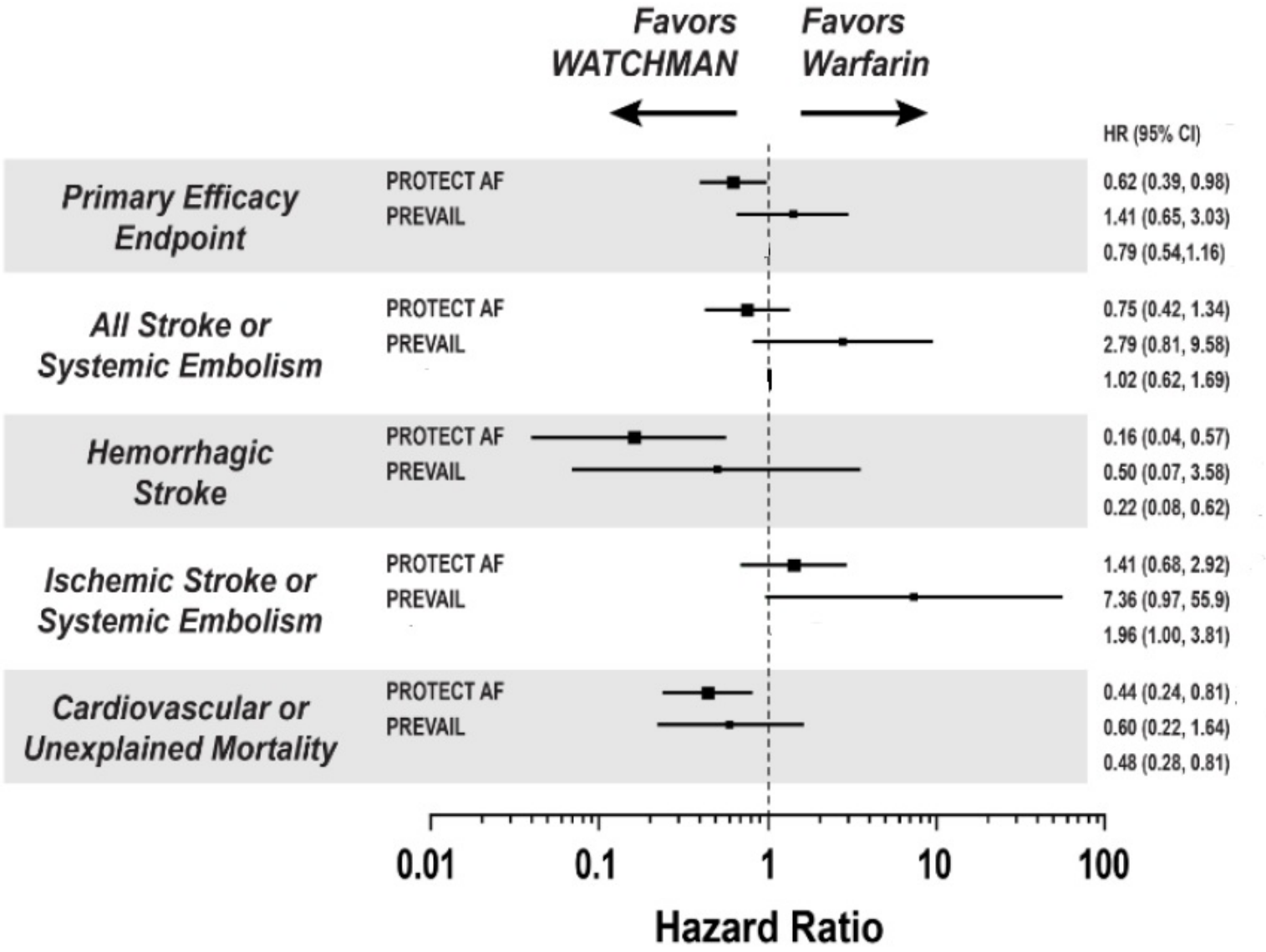
apixiban has similar efficacy and better safety?

but **beware of indirect comparisons**

between-trial differences in:

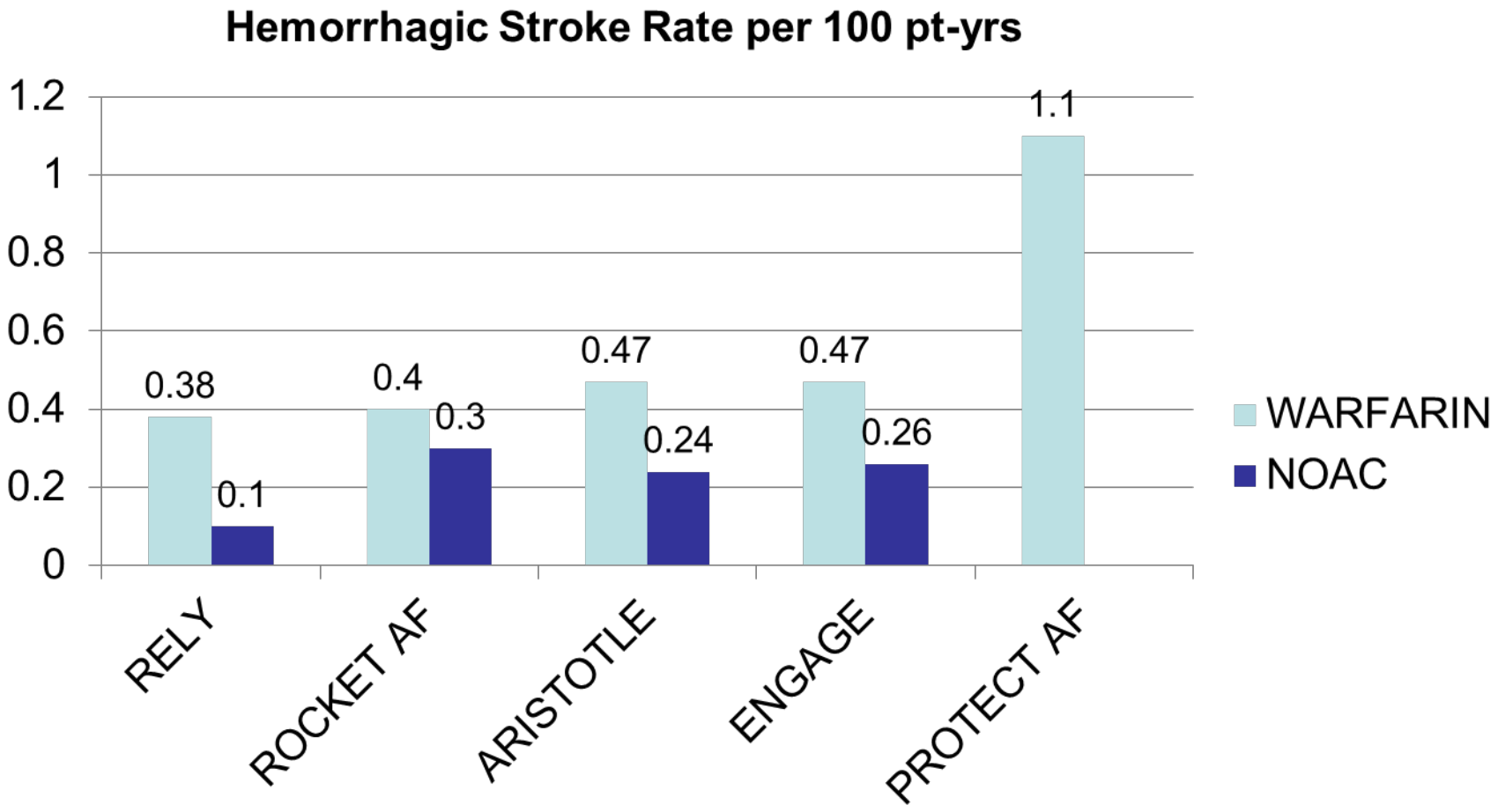
patient selection
outcome definition
blinding (RE-LY was not double blind)
INR control on warfarin
choice of dose

Trial directly comparing new anticoagulants? Unlikely


Favors WATCHMAN
Favors Warfarin
HR (95% CI)
Primary Efficacy Endpoint
PROTECT AF
PREVAIL
0.62 (0.39, 0.98)
1.41 (0.65, 3.03)
0.79 (0.54,1.16)
All Stroke or Systemic Embolism
PROTECT AF
PREVAIL
0.75 (0.42, 1.34)
2.79 (0.81, 9.58)
1.02 (0.62, 1.69)
Hemorrhagic Stroke
PROTECT AF
PREVAIL
0.16 (0.04, 0.57)
0.50 (0.07, 3.58)
0.22 (0.08, 0.62)
Ischemic Stroke or Systemic Embolism
PROTECT AF
PREVAIL
1.41 (0.68, 2.92)
7.36 (0.97, 55.9)
1.96 (1.00, 3.81)
Cardiovascular or Unexplained Mortality
PROTECT AF
PREVAIL
0.44 (0.24, 0.81)
0.60 (0.22, 1.64)
0.48 (0.28, 0.81)
0.01
0.1
1
10
100
Hazard Ratio

Contemporary Anticoagulation Trials

Warfarin and NOAC Treatment Groups



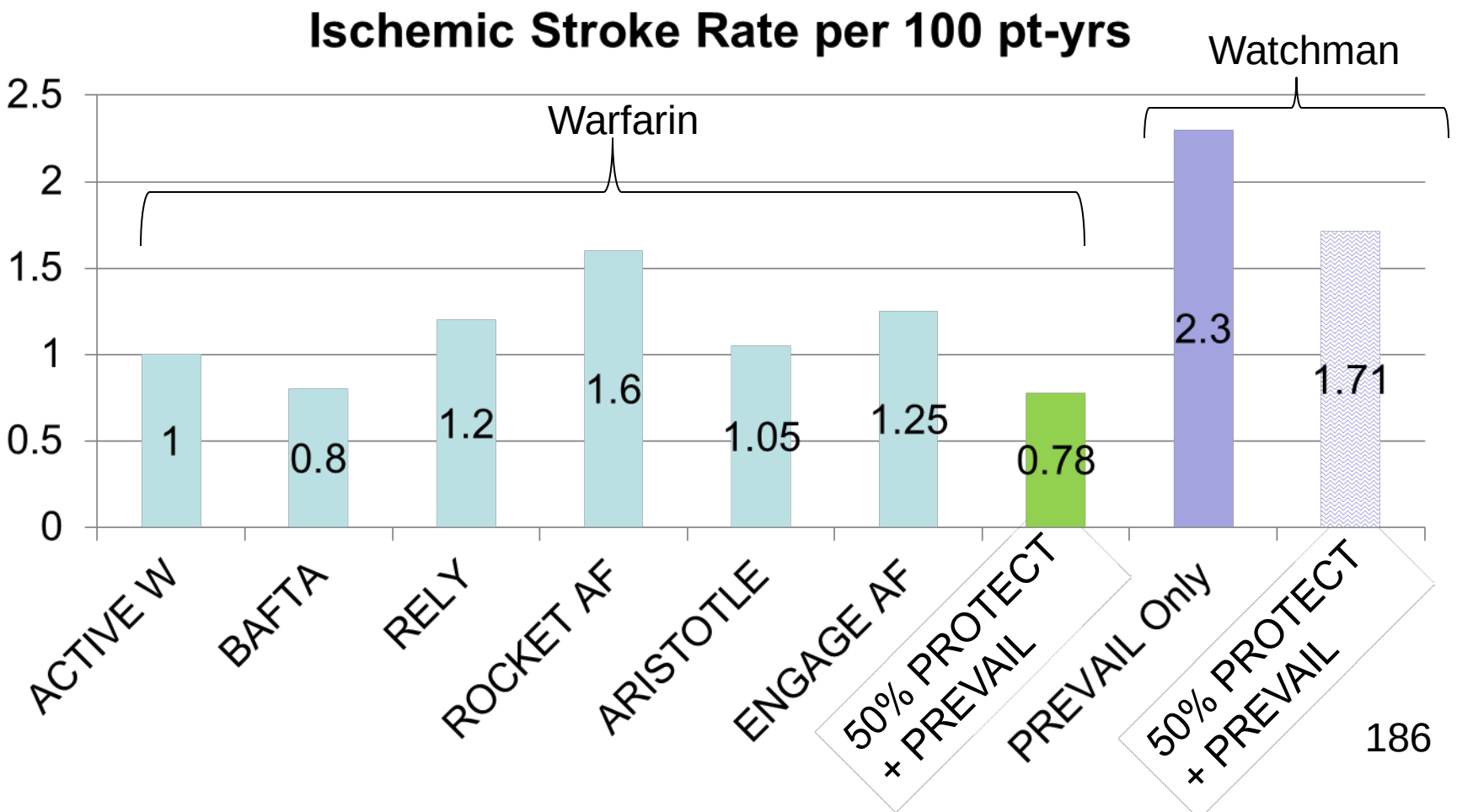
TTR and CHADS2 Scores from Contemporary Anticoagulation Trials

TTR (%)	
ACTIVE W	64
RELY	64
BAFTA	67
ROCKET	55
ARISTOTLE	62
ENGAGE	68
PROTECT	70
PREVAIL	68

Mean $CHADS_2$	
ACTIVE W	2.0
RELY	2.1
ROCKET	3.5
ARISTOTLE	2.1
ENGAGE	2.8
PROTECT	2.3
PREVAIL	2.6

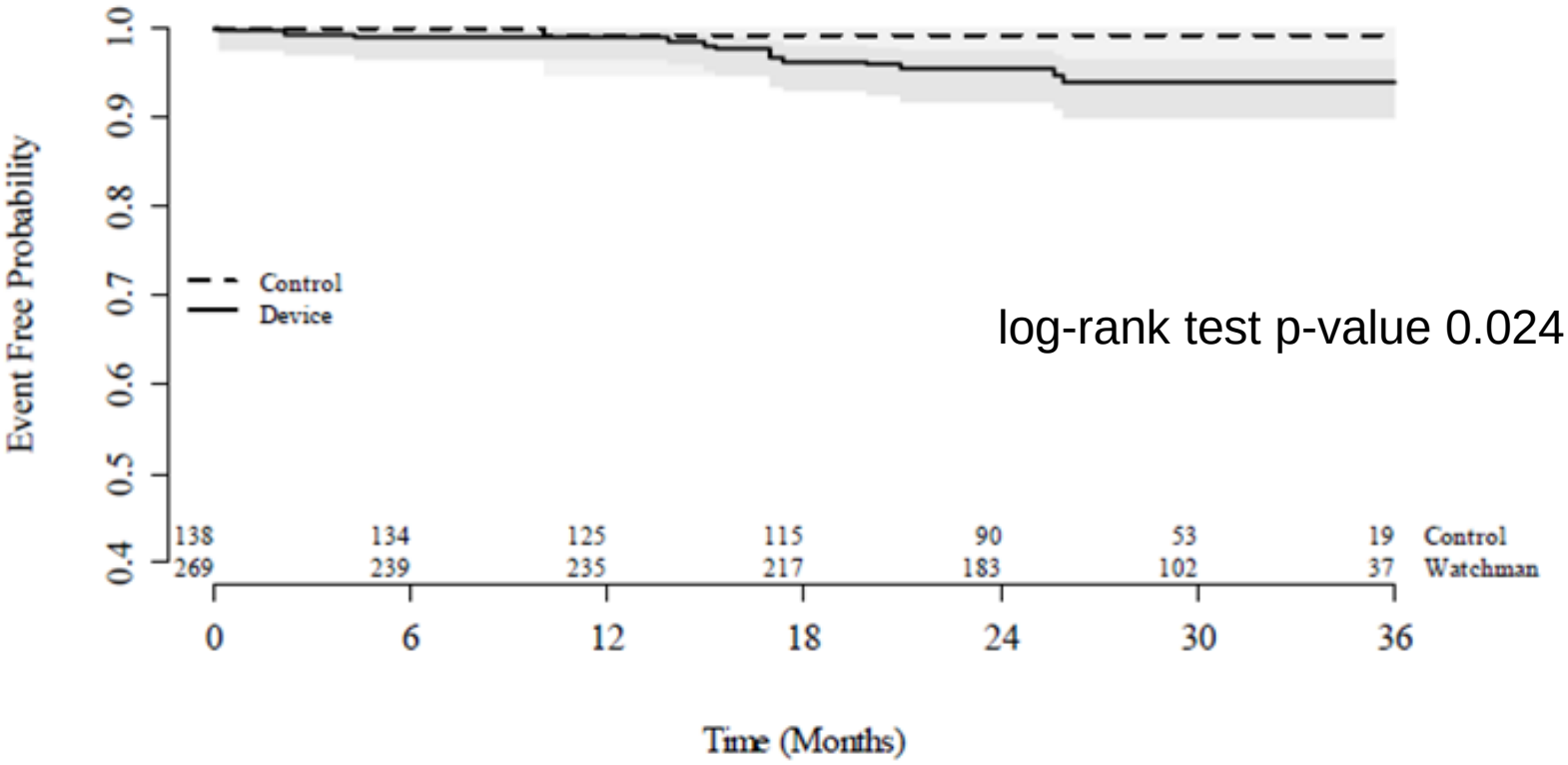
Contemporary Anticoagulation Trials

Warfarin Treatment Groups vs. Watchman



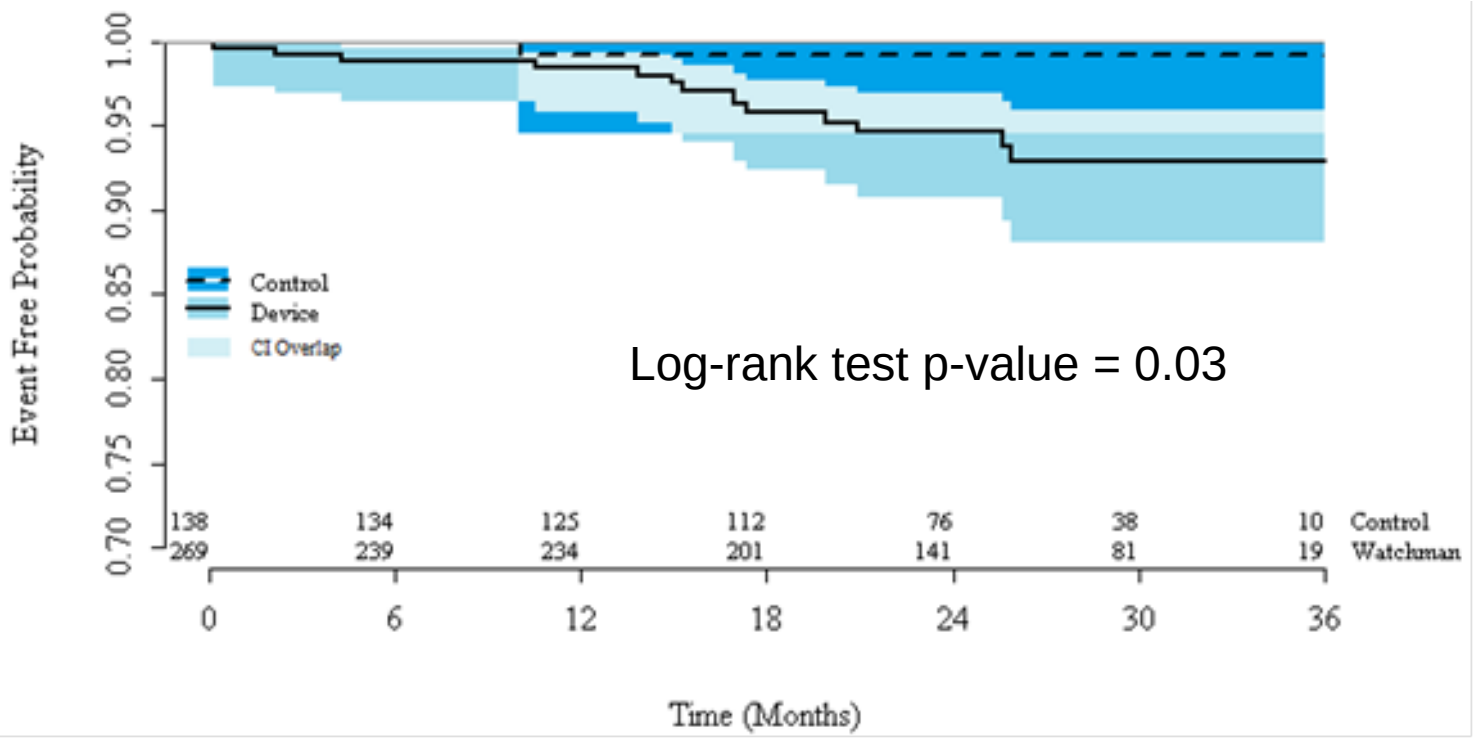
PREVAIL Only

Freedom from Ischemic Stroke



PREVAIL Only

Freedom from Ischemic Stroke or Systemic Embolism



Stats Back-up

The first primary endpoint – Results

Bayesian Approach	Device 18-Month Rate (95% CrI)	Control 18-Month Rate (95% CrI)	18-Month Rate Ratio (95% CrI)	Prior/Posterior Prob. of Non-inferiority
The prior after 50% discount	0.062 (0.034, 0.099)	0.077 (0.040, 0.126)	0.884 (0.374, 1.800)	97.1%
PREVAIL data only / June 2014	0.067 (0.043, 0.097)	0.041 (0.019, 0.072)	1.84 (0.803, 3.851)	54.4%
Posterior (Prior + PREVAIL data)	0.065 (0.045, 0.088)	0.057 (0.035, 0.083)	1.21 (0.69, 2.05)	92.6%

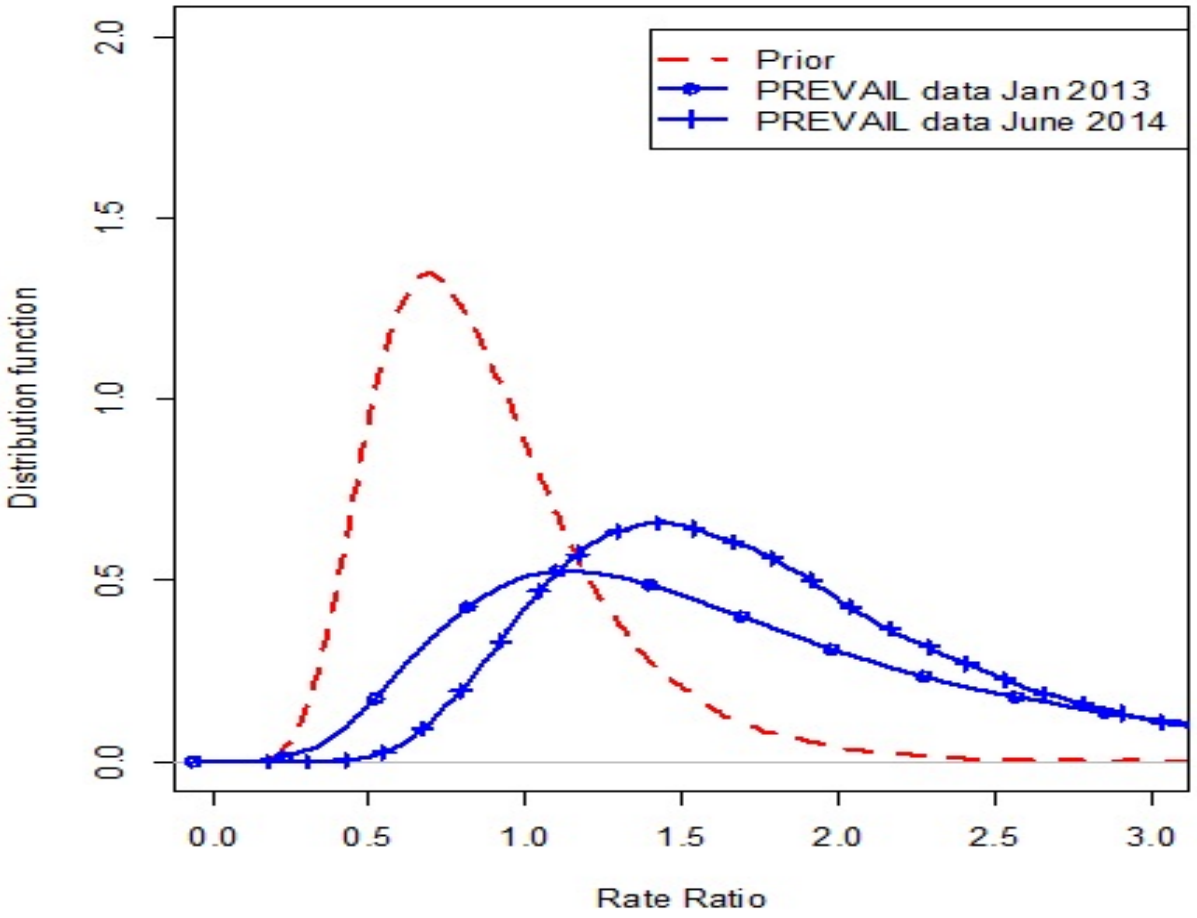
The first primary endpoint – Results

Bayesian Approach	Device 18 Month Rate (95% CrI)	Control 18 Month Rate (95% CrI)	18 Month Rate Ratio (95% CrI)	Prior/Posterior Prob. of Non-inferiority
The prior without 50% discount	0.062 (0.041, 0.087)	0.077 (0.049, 0.111)	0.843 (0.469, 1.404)	99.7%
The prior after 50% discount	0.062 (0.034, 0.099)	0.077 (0.040, 0.126)	0.884 (0.374, 1.800)	97.1%
PREVAIL data only Jan. 2013	0.070 (0.038, 0.112)	0.047 (0.013, 0.102)	2.00 (0.561, 5.830)	56.3%
PREVAIL data only June 2014	0.067 (0.043, 0.097)	0.041 (0.019, 0.072)	1.84 (0.803, 3.851)	54.4%

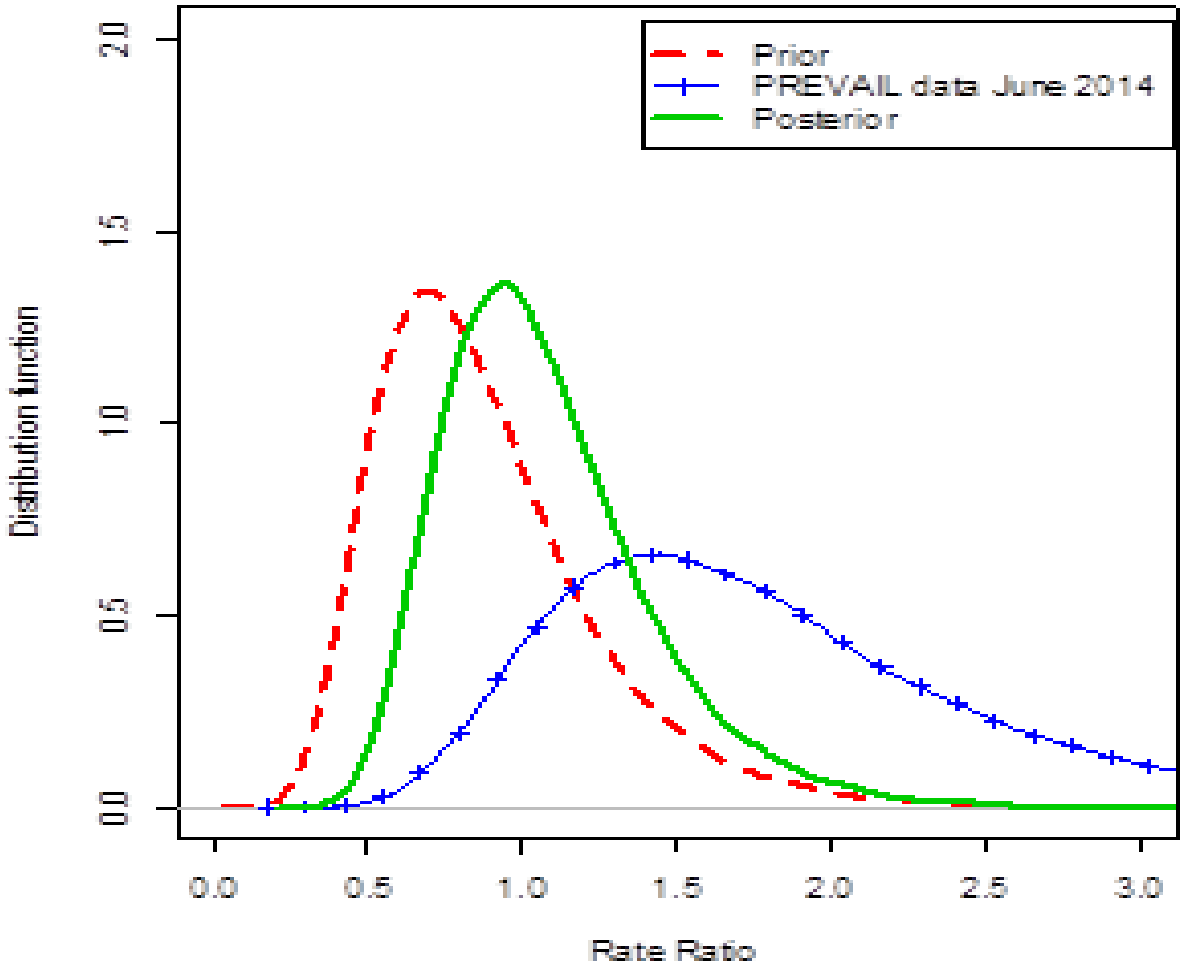
The first primary endpoint – Results

Date of Dataset	Device 18 Month Rate	Control 18 Month Rate	18 Month Rate Ratio (95% CrI)	Posterior Prob. of non-inferiority (FDA analysis)
January 2013	0.064	0.063	1.07 (0.57, 1.89)	95.69%
June 2014	0.065	0.057	1.21 (0.69,2.05)	92.60%

The first primary endpoint – 18-month Rate Ratio Distribution (PROTECT AF prior vs. PREVAIL only)



The first primary endpoint – 18-month Rate Ratio Distribution



The second primary endpoint – Results

Bayesian Approach	Device 18-Month Rate (95% CrI)	Control 18-Month Rate (95% CrI)	18-Month Rate Ratio (95% CrI)	Prior/Posterior Prob. of Non-inferiority
The prior after 50% discount	0.025 (0.009, 0.050)	0.025 (0.007, 0.055)	0.0003 (-0.0341,0.0318)	95.7%
PREVAIL data only / June 2014	0.033 (0.017, 0.053)	0.004 (0.000, 0.016)	0.0284 (0.0097, 0.0499)	48.8%
Posterior (Prior + PREVAIL data)	0.029 (0.017, 0.044)	0.013 (0.004, 0.027)	0.0163 (-0.0023, 0.0342)	89.5%

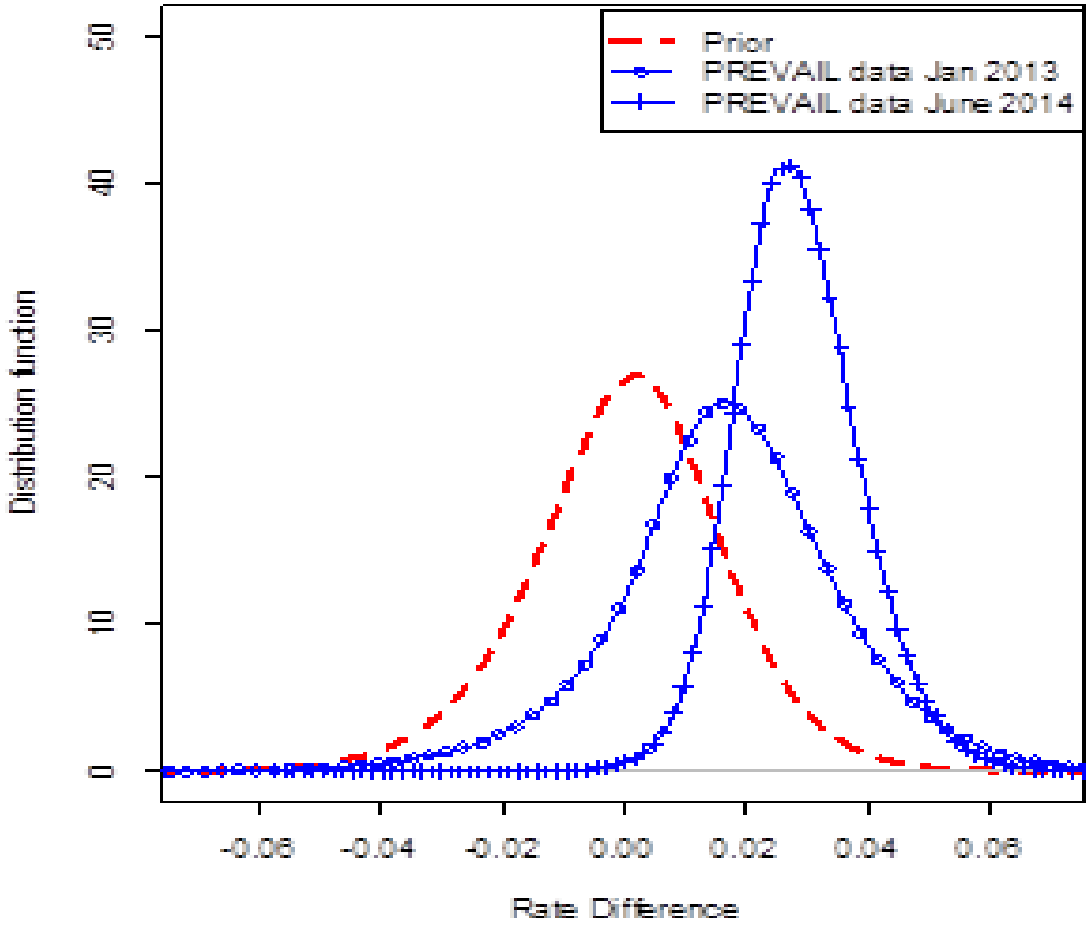
The second primary endpoint – Results

	Device 18 Month Rate (95% CrI)	Control 18 Month Rate (95% CrI)	18 Month Rate Diff. (95% CrI)	Prior/Posterior Prob. of Non-inferiority
The prior before 50% discount	0.025 (0.013, 0.042)	0.025 (0.011, 0.045)	0.0003 (-0.0236,0.0226)	99.1%
The prior after 50% discount	0.025 (0.009, 0.050)	0.025 (0.007 0.055)	0.0003 (-0.0341,0.0318)	95.7%
PREVAIL data only Jan. 2013	0.030 (0.010, 0.062)	0.013 (0.000, 0.049)	0.0167 (-0.0243,0.0538)	73.6%
PREVAIL data only June 2014	0.033 (0.017, 0.053)	0.004 (0.000, 0.016)	0.0284 (0.0097, 0.0499)	48.8%

The second primary endpoint – Results

Date of Dataset	Device 18 Month Rate	Control 18 Month Rate	18 Month Rate Ratio (95% CI) *	Post. Prob. of Non-Inferiority* (FDA analysis)	18 Month Rate Difference (95% CrI)**	Post. Prob. of Non-Inferiority** (FDA analysis)
January 2013	0.0253	0.0200	1.6 (0.5, 4.2)	77.2%	0.0053 (-0.0190, 0.0273)	97.6%
June 2014	0.0294	0.0131	2.8 (0.9, 7.3)	37.3%	0.0163 (-0.0023, 0.0342)	89.5%

The second primary endpoint – 18-month Rate Difference Distribution (PROTECT AF prior vs. PREVAIL only)



The second primary endpoint – 18-month Rate Difference Distribution